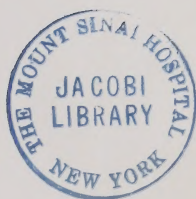




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CONTENTS OF VOLUME XXXV

NUMBER 1, JANUARY-FEBRUARY, 1968

	PAGE
PROGNOSIS OF GRANULOMATOUS COLITIS WITH ONSET IN CHILDHOOD. <i>Burton I. Korelitz, M.D.</i>	1
CONGENITAL ABNORMALITIES OF THE SMALL BOWEL. <i>John E. Moseley, M.D., and Jack G. Rabinowitz, M.D.</i>	14
THIO-TEPA AND METHOTREXATE CHEMOTHERAPY OF ADVANCED OVARIAN CARCINOMA. <i>Ezra M. Greenspan, M.D.</i>	52
THERAPY WITH RADIOISOTOPES: A GENERAL SURVEY (EXCLUDING IODINE). <i>Louis R. Wasserman, M.D., and Joseph L. Glass, M.D.</i>	68
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Klion, M.D., Editor</i> PANCYTOPENIA AND CHRONIC PULMONARY DISEASE IN AN ELDERLY MALE.....	86
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey M. Peck, M.D., Editors</i> EGGSHELL FOREIGN BODY IN SUBGLOTTIC REGION EVIDENT ON CHEST ROENTGENOGRAM.....	98
BILATERAL WILM'S TUMORS.....	100
RECURRENT SMALL BOWEL MYOSARCOMA.....	102
PEDUNCULATED ADENOMATOUS POLYP AT THE LIGAMENT OF TREITZ....	104
ANNOUNCEMENT: RALPH COLP AWARD WINNER. <i>Claude Bloch, M.D., and Harvey M. Peck, M.D.</i>	107
OBITUARY: SERGEI FEITELBERG, M.D.....	108

NUMBER 2, MARCH-APRIL, 1968

HIGH FLOW WHOLE BODY HEMODILUTION PERFUSION: ACID BASE, RENAL, ELECTROLYTE AND BODY FLUID ALTERATIONS. <i>Melvin Kahn, M.D., Berney Goodman, M.D., Robert S. Litwak, M.D., and Howard L. Gadboys, M.D.</i>	111
DIABETIC NEUROPATHY OF THE UPPER EXTREMITIES. <i>Max Ellenberg, M.D.</i> ...	134
RELATIONSHIPS OF RECENT CORONARY ARTERY OCCLUSION AND ACUTE MYOCARDIAL INFARCTION. <i>Irving Chapman, M.D.</i>	149
PEDIATRIC ASPECTS OF ORGANELLE PATHOLOGY OF THE LIVER. <i>Hans Popper, M.D.</i>	155
THROMBOTIC THROMBOCYTOPENIC PURPURA AND SYSTEMIC LUPUS ERYTHEMATOSUS: REPORT OF A CASE WITH IMMUNOFLUORESCENT INVESTIGATION OF VASCULAR LESIONS. <i>Laurence I. Alpert, M.D.</i>	165
ISOENZYMES OF CREATINE PHOSPHOKINASE DETERMINED BY ACRYLAMIDE GEL ELECTROPHORESIS. <i>Arthur H. Wolintz, M.D., W. King Engel, M.D., and Thomas F. Summers, B.S.</i>	174
BUCCAL ANDROSTERONE THERAPY OF HIRSUTISM: A PRELIMINARY REPORT. <i>Solomon I. Griboff, M.D., and Walter Futterweit, M.D.</i>	179

CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Klion, M.D., Editor</i>	
FEVER, HEPATOSPLENOMEGALLY AND PULMONARY DENSITIES.....	184
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey M. Peck, M.D., Co-Editors</i>	
ANEURYSMAL BONE CYST WITH DOCUMENTED SUBPERIOSTEAL ORIGIN.....	192
URETEROCELE, DUPLEX COLLECTING SYSTEM, AND OBSTRUCTIVE UROPATHY.....	196
GASTRIC LEIOMYOSARCOMA WITH REMARKABLE PROGRESS OVER A TWO YEAR PERIOD.....	199
CHRONIC OSTEOMYELITIS BRODIE'S ABSCESS.....	206
NUMBER 3, MAY-JUNE, 1968	
OBITUARY. <i>Bela Schick, M.D.</i>	211
CRIB DEATHS: THEIR POSSIBLE RELATIONSHIP TO POST-PARTUM DEPRESSION AND INFANTICIDE. <i>Stuart S. Asch, M.D.</i>	214
THE HISTORY OF CAROTID ARTERY LIGATION. <i>Sidney W. Gross, M.D.</i>	221
THE TEMPOROMANDIBULAR JOINTS: A SURVEY OF DISORDERS AND TREATMENT METHODS. <i>Jack Klatell, D.D.S., and Joseph J. Marbach, D.D.S.</i>	228
EARLY RESULTS WITH TWENTY FEMORO-POPLITEAL VEIN BYPASS GRAFTS FOR SEVERE PERIPHERAL ISCHEMIA. <i>Adolf Singer, M.D., and Giuseppi Rossi, M.D.</i>	234
METASTATIC INFILTRATION OF THE THYROID GLAND CAUSING HYPOTHYROIDISM. <i>David K. Sirota, M.D., Edythe B. Goldfield, M.D., Young F. Eng, M.D., and Allen H. Unger, M.D.</i>	242
PSYCHOTHERAPEUTIC DRUGS—PATTERNS OF USE. <i>Joanna Magda Polenz, M.D., and Samuel L. Feder, M.D.</i>	246
COOMBS' POSITIVE HEMOLYTIC ANEMIA DUE TO PENICILLIN. <i>Leonard J. Lyon, M.D.</i>	258
EXERCISE IN NORMAL DOGS UNDER CHLORALOSE AND URETHANE ANESTHESIA. <i>Paul D. Stein, M.D., Douglas Allen, M.D., George Gabor, M.D., and Richard P. Lasser, M.D.</i>	265
BONE TUMORS OF PERIOSTEAL ORIGIN. <i>Robert Zaretsky, M.D.</i>	274
UNUSUAL PROBLEMS IN SURGERY. <i>A. Robert Beck, M.D., Lewis Burrows, M.D., and Julius J. Leichtling, M.D., Editors</i>	287
INDIRECT TRAUMATIC DIAPHRAGMATIC HERNIA. TYPICAL AND UNUSUAL FEATURES IN TWO CASES.....	287
GASTRIC PERFORATION IN A NEWBORN.....	300
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Klion, M.D., Editor</i> ...	307
JUVENILE DIABETES MELLITUS, RHEUMATIC HEART DISEASE, FEVER, AND MASSIVE HEMOPTYSIS.....	307
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey Peck, M.D., Co-Editors</i>	
CARCINOMA IN SIGMOID BLIND LOOP.....	318
SMALL BOWEL POSTOPERATIVE BLIND LOOP CAUSING ANEMIA.....	321
COLONIC BEZOAR DUE TO SERUTAN.....	323

JEJUNAL SUBMUCOSAL HEMORRHAGE FOLLOWING ANTICOAGULANT THERAPY.....	328
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NUMBER 4, JULY-AUGUST, 1968

OBITUARY: <i>Dr. Howard L. Gadboys</i>	329
CURRENT TRENDS IN CURRICULUM REDESIGN. <i>Hans Popper, M.D.</i>	332
CONTRALATERAL TRIGEMINAL NEURALGIA IN MENINGIOMAS OF THE CEREBELLO-PONTINE ANGLE. <i>Philip Levin, M.D. and Sidney Gross, M.D.</i> ...	343
THE RESPONSIBILITY OF BEING AN OBSTETRICIAN AND GYNCOLOGIST. <i>Marcel Heiman, M.D.</i>	350
INSTITUTIONAL CARE FACILITIES FOR OLDER PEOPLE IN NEW YORK CITY. <i>Martha Rogin, Alvin I. Goldfarb, M.D., and Helen Turner</i>	358
EVOLUTION AND PATHOGENESIS OF DISCOGENIC SPINE PAIN AND ASSOCIATED RADICULITIS AS SEEN IN THE NEW YORK CITY FIRE DEPARTMENT. <i>Albert J. Schein, M.D.</i>	371
RADICAL LOCAL SURGERY IN DIABETIC GANGRENE. <i>Adolf Singer, M.D. and Giuseppe Rossi, M.D.</i>	390
INTRAPERITONEAL HEMORRHAGE AS A COMPLICATION OF ACUTE RUPTURED CHOLECYSTITIS. <i>Mahmood A. Naqvi, M.D., Callisto A. Danese, M.D., and David A. Dreiling, M.D.</i>	396
MINIMAL LEGG-CALVE-PERTHES DISEASE. <i>Jacob F. Katz, M.D.</i>	408
INTESTINAL OBSTRUCTION CAUSED BY EXTRINSIC BENIGN MYOMATA. <i>Irving H. Parnes, M.D.</i>	417
THE INITIAL CONTACT WITH THE CANCER PATIENT—SOME PSYCHIATRIC CONSIDERATIONS. <i>Richard S. Blacher, M.D. and Charles Winkelstein, M.D.</i>	423
THE EFFECT OF VARYING FAT DIETS ON THE INCORPORATION OF FATTY ACIDS INTO ESTERS BY THE SMALL INTESTINE IN VITRO. <i>Alvin M. Gelb, M.D.</i> ...	429
RADIOLOGICAL NOTES, <i>Claude Bloch, M.D. and Harvey M. Peck, M.D., Co-Editors</i>	
FAMILIAL FIBROSIS OF THE JAW (CHERUBISM). <i>Submitted by Ralph Lachman, M.D.</i>	436
ASPHYXIATING THORACIC DYSTROPHY. <i>Submitted by Ralph Lachman, M.D.</i>	438
EXTRAPLEURAL NEUROFIBROMA. <i>Submitted by Samuel Andelman, M.D.</i> ...	443
EXTRAPLEURAL LIPOMA. <i>Submitted by Samuel Andelman, M.D.</i>	444
ANEURYSM OF THE SPLENIC ARTERY MIMICKING AN INTRAMURAL TUMOR OF THE STOMACH.	447

NUMBER 5, SEPTEMBER-OCTOBER, 1968

DEVELOPMENT AND GOALS OF A TRAUMA AND SHOCK RESEARCH CENTER. <i>William C. Shoemaker, M.D., David H. Elwyn, M.D., and Arthur L. Rosen, M.D.</i>	451
CONCEPTS AND TREATMENT IN POLYMYALGIA RHEUMATICA. <i>Selvan Davison, M.D., and Harry Spiera, M.D.</i>	473

TUBERCULOUS MEDIASTINAL ADENOPATHY SIMULATING NEOPLASM. <i>Jack G. Rabinowitz, M.D., and Irwin Gribetz, M.D.</i>	479
WRIST-CUTTING AND SUICIDE. <i>Carl Rinzler, M.D., and David A. Shapiro, M.D.</i>	485
THE BASSEN-KORNZWEIG SYNDROME: <i>Robert M. Sturman, M.D.</i>	489
BILATERAL COMPLETE INTERNAL CAROTID ARTERY OCCLUSIONS IN A PATIENT WITH TRANSIENT NEUROLOGIC DEFICITS. <i>Lawrence D. Jacobs, M.D.</i>	518
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Klion, M.D., Editor</i>	
JAUNDICE AND CONGESTIVE FAILURE AFTER CARDIAC VALVE REPLACEMENT.....	526
UNUSUAL PROBLEMS IN SURGERY. <i>A. Robert Beck, M.D., Lewis Burrows, M.D., and Julius J. Leichtling, M.D., Editors.</i>	
SPLENOSIS AND INTESTINAL OBSTRUCTION.....	534

NUMBER 6, NOVEMBER-DECEMBER, 1968

CORONARY ARTERY DISEASE: REST, REPAIR, OR REPLACEMENT. <i>Dwight E. Harken, M.D.</i>	541
AFEBRILE BACTERIAL ENDOCARDITIS. A CLINICAL STUDY OF TWO CASES. <i>Eugene M. Teich, M.D.</i>	566
EOSINOPHILIC MENINGITIS: REPORT OF TWO UNUSUAL CASES. <i>Seymour Gendelman, M.D.</i>	578
DIABETIC NEUROPATHIC ULCER. <i>Max Ellenberg, M.D.</i>	585
PROBLEMS OF STERILIZATION. <i>Emanuel Klempner, M.D.</i>	595
AN INCISION AND METHOD OF WOUND CLOSURE FOR RADICAL MASTECTOMY. <i>Gerson J. Lesnick, M.D.</i>	599
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Klion, M.D., Editor</i>	
SICKLE CELL ANEMIA COMPLICATED BY ANURIA.....	610
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey M. Peck, M.D., Co-Editors</i>	
GASTRIC POLYPS-LONG-TERM FOLLOW-UP. REPORT OF TWO CASES. <i>Submitted by Rhona J. Keller, M.D.</i>	622
GASTRIC CARCINOMA: 3½ YEAR FOLLOW-UP.....	630
METASTATIC LESION OF THE COLON—PRIMARY IN THE STOMACH.....	635
METASTATIC LESIONS TO THE COLON—REPORT OF THREE CASES.....	639
INDEX TO VOLUME XXXV.....	645

Prognosis of Granulomatous Colitis with Onset in Childhood

BURTON I. KORELITZ, M.D.

The division of *inflammatory disease of the colon* into the granulomatous and ulcerative exudative types has been suggested by clinical factors and now defined by extensive pathological study (1) and by distinguishing radiological features (2). Utilizing these three kinds of criteria, 25 children who had onset of granulomatous colitis (Crohn's disease of the colon) before age 16 were identified among 470 cases with inflammatory disease of the colon. These patients have been traced to determine the extended clinical course, results of surgical procedures and status at follow-up, in order to clarify the proper management.

Patients

The 25 children were admitted to The Mount Sinai Hospital at some time between 1936 and 1964. These represent approximately 15 per cent of all patients in the same age group admitted during the same period of time and formerly grouped under the terminology *ulcerative colitis*. They also represent approximately 24 per cent of patients of all ages with granulomatous colitis. The mean age at recognizable onset of the disease was 13 with a range of 7 to 15. There were 16 females and 9 males. The granulomatous nature of the disease was confirmed by pathological examinations of the colon or ileum in 11 of 17 surgical cases; in the other 6 the colon was grossly, as well as clinically or radiologically granulomatous, though the essential histological features were not described. Of the remaining 8 patients treated medically without surgical intervention, all had both radiological and clinical features of granulomatous disease.

The living patients have either been followed through the Mount Sinai Hospital or private practice or traced by various methods in order to obtain detailed information from gastroenterologists, surgeons and hospital records about the later course since the last hospital admission. Pertinent details of late results until at least 1965 were collected. The length of follow-up was only two years in one case but 5 to 30 years, with a mean of 17, in the others.

RESULTS

Clinical features

The more common primary manifestations of the disease determined by history or physical examination prior to definitive surgery are noted in Table

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1. In one patient the diagnosis of rheumatic fever was made at the onset. In another a hemorrhoidectomy was performed before the true nature of her disease was recognized. Two patients were surgically explored and had appendectomy performed near the onset.

Complications

Local and systemic complications of the disease occurred in 21 of the 25 cases prior to any surgery and still new complications followed definitive surgery in 13 of the 17 so treated. These are listed in Table 2. One patient had coincident rheumatic heart disease. Two female patients in the fourth decade developed cholecystitis at some time after definitive surgery for the primary disease.

Extent of disease

Table 3 shows the distribution of colonic involvement prior to surgical intervention and whether and to what extent the small bowel was involved. These findings were determined by x-ray and surgical exploration in 17 cases, by x-ray alone in 7, and by postmortem examination in 1 case. In all 25 cases the rectal mucosa was free of any sign of active inflammatory disease as determined by sigmoidoscopy performed by the attending gastroenterologist prior to steroid therapy or surgical intervention.

Medical management

In 13 cases the general therapeutic measures of sedation, enforced nutrition, infusion, transfusion and utilization of opiates and sulfonamide drugs were supplemented with adrenocorticotrophic hormone or adrenal steroids. These included 7 of the 8 nonsurgical cases and 6 of the 17 patients who required surgery. Ten of the remaining 11 surgical cases had been operated upon in the pre-steroid era.

Of the 7 medical cases treated with steroids, 6 improved. Hormonal therapy was continued for a few months up to seven years; at the time of follow-up 5 of the 6 were well, 2 still receiving steroids after 6 or 7 years, while in 4 the steroids had been stopped for from 1½ to 12 years. One patient died while on steroids after two years of disease.

At least 2 patients have had prolonged remissions coincident with Salicylazosulfapyridine (Azulfidine) therapy.

Of the 6 surgical cases treated with steroids, there had been improvement for months to 6 years before a complication led to surgical intervention. Two of these patients once again improved with steroids at the time of an exacerbation following an ileocolostomy.

Indications for surgery

Of the 25 patients in this study, 17 (68%) required major surgical intervention. The duration of the preoperative period varied from a few months

to 12 years with a mean of 4 years. The mean preoperative period for those not treated with steroids, however, was 3 years (11 cases) as opposed to 7.5 years (6 cases) for those that were treated with steroids.

The major and supplementary indications for surgical intervention are shown in Table 4. The indications for later major operative procedures are also tabulated.

Initial and secondary operative procedures

There were 45 definitive and major procedures performed in 17 patients. The nature of these operations and the order in which they were performed are shown in Table 5. In 9 of the 17 patients there were secondary major and minor nondefinitive operations performed because of complications. These included incision and drainage of abscesses in 15, lysis of adhesions in 3, ileostomy revisions in 7 (5 in one patient), and 4 others. Table 6 shows the total numbers of operations per patient.

Extension of disease distally

Of the 8 medically treated patients, 7 are alive and in none has there been sigmoidoscopic evidence of mucosal involvement in the rectal segment. The 17 surgically treated patients have not fared as well (shown in Table 7).

Extension of disease proximally

In the 8 medically treated patients there was no extension of disease proximally. Again the results differed in those who had been treated surgically (Table 7).

Time until extension of disease after surgery

In only one instance was there spread of disease to the rectal segment prior to surgery. In 9 other cases the extension occurred at a time varying from months after the surgical procedure to 14 years. Though the mean period was 2 years, in 4 cases the rectum remained free of disease for 7 years or more. In 2 cases the extension followed ileostomy and subtotal colectomy and in the other 7 cases extension occurred after ileocolostomy, all but one with resection.

In 8 cases there was extension of disease to the new terminal ileum after surgery was performed, varying in time from weeks to 11 years, with an average of 4.5 years. The spread of disease followed ileocolostomy with resection in 5 cases, ileocolostomy without resection in 2 cases and ileostomy and subtotal colectomy in another. There was still further proximal extension of disease following secondary ileocolostomy with resection in 2 cases (one immediate; one after 5 years), after ileo-ileostomy in 2 cases (one immediate; one after a year) and in 2 cases after ileostomy. One patient had a reanastomosis (ileoproctostomy) which has endured for 20 years despite proximal extension, intestinal obstruction by adhesions and need for dilatation of recurrent rectal stricturing.

Late results and recent status

The data are shown in Table 8. Of the eight medically treated patients, one 16-year-old boy died. While receiving ACTH intravenously he developed infection at the cut-down site followed by staphylococcal septicemia, thrombophlebitis, pulmonary embolism, pulmonary edema and preterminal massive upper gastrointestinal hemorrhage. One developed a fistula from the hepatic flexure to the transverse duodenum and is about to have surgery; one developed a slowly burrowing perirectal fistula which improved after conservative local surgery; one developed 2 strictures and has occasional fever; and one still requires steroid therapy and his growth is retarded. Only 3 have been well for prolonged periods (6, 7 and 12 years) without requiring treatment. In no case, however, has there been extension of disease to the rectal segment.

Of the 17 surgically treated patients, 3 have died. In one 18-year-old boy a second ileocolostomy performed for an abdominal abscess and vesicocolonic fistula was followed by intestinal obstruction. An emergency ileostomy was performed but he died with peritonitis. A 19-year-old boy, following an abdominoperineal resection, developed peri-ileostomy infection and a fecal fistula to the perineum. He died of sepsis following exploration of the abdominal wound. Both of these deaths occurred before the discovery of antibiotics. A 39-year-old woman died with toxic dilation of the colon during a severe exacerbation of disease after having been essentially symptom-free since an internal anastomosis without resection that had been performed in childhood. In addition to the 2 patients with ileostomies who died, 3 of the 6 remaining alive have had extension of disease to the new terminal ileum and only one has been truly symptom-free for 5 years. There are 8 patients who still have ileocolostomies but only 2 have had no extension of disease either distally or proximally and been well more than 5 years (8 and 29 years).

The influence of the original extent of involvement on later results: The data in Table 9 show that those cases where granulomatous disease involved the ileum as well as the colon had a much poorer prognosis than those in which the ileum was free of disease.

Pathological features

Of the 16 surgical specimens, histologic evidence of granulomatous disease was found in 11—in all except 1 in the colon itself. In the eleventh case, the granulomata were found in a specimen of ileum after ileostomy revision for recurrent disease, while the colon examined following an earlier operation was more consistent with ulcerative colitis. In no case were granulomata found in the rectal segment removed by abdominoperineal resection. In 2 cases granulomata were found in mesenteric lymph nodes. In 5 cases the colon was grossly thickened and usually associated with a mass at exploration but histologically was reported as ulcerative colitis. In 3 of these (and another 3 with granulomata histologically) linear ulcerations were described.

Radiological features

While in a few cases x-ray findings were not sufficiently characteristic to differentiate granulomatous from ulcerative colitis, the sparing of the rectum in itself favored the former diagnosis. In most cases one or more of the specific radiological features of granulomatous disease as described by Wolf and Marshak were noted. These included skip areas, internal fistula formation, some strictures, eccentric mucosal involvement—some with prominent pseudodiverticula, marked mucosal nodularity or thumb printing and longitudinal or linear ulcerations. Characteristic transverse fissures were rarely seen, but in many cases old x-ray films were unavailable for review.

DISCUSSION

Until recently it had been observed that approximately 8 per cent of cases of ulcerative colitis were predominantly right-sided and most of these cases were defined as *regional* or *segmental*. Introduction of the pathological concept of Crohn's disease of the colon by Lockhart-Mummery and Morson has led to greater efforts by surgical pathologists to distinguish this granulomatous disease from ulcerative colitis in surgical specimens. As a result it has become clear that the vast majority of previously reported cases in which the rectum was at least initially free of disease were undoubtedly instances of granulomatous colitis (3). In the most common examples of this disease, the only site or the most advanced site of colonic involvement will be the right colon, usually with associated disease of the terminal ileum which appears radiologically similar to regional ileitis. The capacity of more distal segments to show the same pathological response however has been clearly demonstrated. At St. Marks Hospital the incidence of rectal disease has been as high as 50 per cent and occasionally the rectum is the only segment involved (1, 4). Why the rectal segment has been far less frequently involved according to studies reported from this country as compared with studies from England has not yet been clarified (5, 6). In the present study of cases with onset in childhood, there was no instance of rectal involvement prior to definitive surgery.

Though ulcerative colitis must still be considered a more prevalent disease than granulomatous colitis, a larger proportion of the latter group has onset of disease during the childhood years. There is also a greater preponderance of female patients.

The most representative clinical picture of granulomatous colitis is that of non-bloody diarrhea, fever and weight loss. Abdominal pain if present is more likely to be right-sided and often associated with a mass. Blood per rectum is often associated with a perirectal complication rather than mucosal inflammation, but massive hemorrhage from sources in the right colon is not uncommon (3). Granulomatous disease may present as fever of unknown origin, perhaps associated with arthritis, erythema nodosum or uveitis, long before the onset of diarrhea.

The occurrence of fistulae from a segment of intestine to another loop of

bowel, to the mesentery, or to the abdominal wall or to a different organ system is itself characteristic of granulomatous disease and is different from ulcerative colitis (7, 8). The incidence of perirectal suppuration and fistulae is higher and large anal ulcerations are unique. Perforations occur but are more likely to be walled off. Colonic strictures are more common, often adjoin skip areas, and occur earlier than in ulcerative colitis; the differential diagnosis from neoplasm is of much less concern in that no case of carcinoma of the colon or rectum has yet been clearly demonstrated as a complication of granulomatous colitis. Following definitive surgery there is still a higher incidence of internal fistulae, rectal stricture, small bowel obstruction and nephrolithiasis than preoperatively. Toxic dilation of the colon, one of the common serious complications of ulcerative colitis, occurs rarely in granulomatous disease, though it was a late complication of one case in this study.

Granulomatous colitis is in general a more insidious disease than ulcerative colitis, and though the incidence of complications is the same (7, 8), these complications are less likely to be acute and require urgent surgery. The results of medical therapy have been disappointing, even more so than in ulcerative colitis, despite the frequent dramatic remission resulting from ACTH and adrenal steroids. Hormonal therapy has not retarded the development of intraabdominal fistula and abscess formation, perirectal complications and obstruction and steroids have increased the likelihood of delayed growth and development. The net result of medical management is no better than that reported by Crohn, Yarnis and Garlock for right-sided colitis 20 years ago (9). ACTH and adrenal steroids have served, however, to postpone the date of surgical intervention.

With indication for surgical intervention, the right-sided distribution of inflammatory disease of the colon has encouraged procedures utilizing the normal rectum and negating the need for ileostomy. Such internal anastomoses would in some cases be successful and in others be followed by extension of disease, often with disastrous results (10). The reasons for this are probably related to the nature of the inflammatory process. If the terminal ileum involved even minimally with regional ileitis should be transected, extension of the disease proximally would be anticipated, whereas the terminal ileum minimally involved with the ileitis associated with ulcerative colitis ("backwash") can be transected with little concern (11). While the terminal ileum involved with regional ileitis can be bypassed (ileocolostomy) with reasonable hope of long-term remission and no extension of disease, a bypass of a segment of colon involved with ulcerative colitis is less likely to fare as well. In theory, colonic disease should be histologically more related to ileitis than to ulcerative colitis for a bypass operation to be performed without resulting in spread of the disease toward the rectum, though with an increased risk of spread proximally into the new terminal ileum.

In this retrospective study it appears that indications for surgery arose with a frequency twice that of ulcerative colitis (7, 8). In considering sur-

gery the existing medical situation must be weighed against the risk of provoking extension postoperatively.

If there are no complications and the indications for surgery are therefore questionable, the high incidence of spread of disease to the new terminal ileum should encourage persistence in a medical program despite its poor results. This is particularly true when the small bowel is involved preoperatively. This attitude is in distinction to treatment of ulcerative colitis where elective surgical intervention is encouraged after an arbitrary period of two years where there are continued manifestations of the primary bowel disease with or without complications (12).

Should serious complications such as obstruction, intraabdominal abscess or marked perirectal suppuration occur, or there be a more chronic but also ominous complication as retarded growth and development, surgical intervention is more clearly indicated. The operative procedure should be varied according to the complication. If there are significant perirectal complications, an ileostomy should be preferred to an ileocolostomy even if the rectal mucosa appears normal. A reanastomosis might be more reasonably considered at a later date in this disease as compared with ulcerative colitis. The likelihood of surviving and not requiring further definitive surgery after an ileocolostomy (with or without resection) because of extension, fistulization, abscess formation, obstruction, hemorrhage, perforation or overall degeneration of health is no better than 35 per cent and in only 14 per cent of patients has there been no complication since the time of surgery. The same considerations are present after failure of the primary surgery in choosing between a second ileocolostomy and ileostomy. But even in patients treated primarily or secondarily with ileostomy, only 1 out of 9 has no further trouble for a prolonged period and 5 out of 9 develop active disease in the new terminal ileum. If feasible, therefore, a trial with an internal shunt procedure is merited, particularly since a new complication or extension of disease proximally may not occur for many years. Although the performance of surgery is an invitation to extension of disease distally in more than half of the cases, the rectal involvement might be minor and need not in itself require further surgical intervention. When granulomatous disease is limited to the colon, the likelihood of long-term surgical cure is greater and adds support to the indications for surgery.

Though the medically treated cases might have been less severe, it is encouraging that even a few can do well and others fairly well on a conservative program. The long-term use of Azulfidine supplemented by periodic steroid therapy seemed to increase the medical salvage rate and in turn improve the overall prognosis.

SUMMARY AND CONCLUSIONS

The course of granulomatous colitis was studied in 25 children with onset before age 16 to determine the natural history and late results. The granulomatous nature was recognized clinically and/or radiologically in all, and of

17 patients (68%) requiring definitive surgery, confirmed histologically in 11 and supported by gross pathological findings in 6. The mean follow-up was 17 years. The disease was predominantly right-sided, including the terminal ileum in 19 and skip areas in 4. The rectum was initially free of disease in all. Growth and development were retarded in 6. There was a high incidence of internal and external fistulae, colonic stricture and obstruction, and nephrolithiasis—in all cases more postoperatively than preoperatively. Steroid therapy resulted in at least temporary improvement and extended postponement of surgery. The outcome of surgery was discouraging in that 17 patients required 71 operations including 45 major definitive procedures. The disease extended to the rectum in 9 after surgery but in only 1 without. In 8 cases there was proximal spread postoperatively after weeks to 11 years. At follow-up 4 had died. Only 3 medically treated patients remained well for 5 years. Eight of 14 still had ileocolostomies; only 2 remained well for 5 years, and without extension either proximally or distally. Of 9 patients requiring ileostomy, 5 had had spread to the new terminal ileum, including 2 who died, and only 1 was symptom-free for 5 years. The prognosis was worse when the terminal ileum was originally involved.

When granulomatous colitis has its onset in childhood, it occurs in perhaps its purest form with sparing of the rectal segment. A larger proportion of patients has onset during childhood and there is a greater preponderance of female patients than in ulcerative colitis. Indications for surgery arise with a frequency almost twice that of ulcerative colitis. Still the high incidence of extension of disease to the new terminal ileum should encourage persistence in a medical program, contrary to the attitude in managing ulcerative colitis. If surgery is to be performed and the rectum is free of disease, an ileocolostomy should be initially favored, since new complications or extension of disease proximally may not occur for a long time thereafter.

Acknowledgment

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TABLE 1
Clinical Features in 25 Cases of Granulomatous Colitis

Symptom or Physical Finding	Present No. Cases	Absent No. Cases	Insufficient Information
Diarrhea	20	4	1
Fever	18		7
Abdominal pain	19		6
Right-sided tenderness	12		
Right lower quadrant mass	3		
Weight loss	10		
Blood per rectum	7*	13	5

* Possibly associated with peri-rectal complications in four cases.

TABLE 2
Local and Systemic Complications in 25 Cases of Granulomatous Colitis

	Before Definitive Surgery (21 of 25 cases) No. Cases	Following Definitive Surgery (13 of 17 cases) No. Cases
Fistulae		
Perirectal	6	4
Internal (from ileum or colon)	7	6
Rectovaginal		3
Abscesses		
Perirectal	4	4
Other	4	6
Anal ulceration	2	1
Colonic perforation	3	1
Ileal perforation		1
Pericolonic abscess	2	
Toxic dilatation of colon		1
Rectal hemorrhage	2	
Colonic stricture	5	4
Rectal stricture		4
Colonic obstruction	2	
Ileal obstruction		6
Obstruction due to adhesions		2
Arthralgia or arthritis	7	1
Erythema nodosum	6	
Clubbing	2	
Retarded growth and development	6	
Thrombophlebitis	1	
Pulmonary emboli	1	
Osteoporosis	1	
Vertebral collapse	1	
Malabsorption	1	
Nephrolithiasis	1	4
Hydronephrosis	1	
Retroperitoneal fibroplasia		1
Gram negative septicemia	1	
Cholecystitis		2
Tenosynovitis	1	
Narcotics addiction		1
Upper G.I. bleeding		1

TABLE 3
Extent of Inflammatory Disease in 25 Patients

	Colonic Involvement (No.)	Terminal Ileum Involvement (No.)
Cecum to sigmoid.....	10 ^s	7*
Cecum to descending.....	1 ^s	1
Cecum to distal transverse.....	1	
Cecum to proximal transverse.....	5	5
Cecum to ascending.....	4 ^s	4*
Ascending to descending.....	2 ^s	1*
Ascending to transverse.....	1	1
Transverse to sigmoid.....	1	—

* More than one foot of ileum involved.

^s Skip areas of normal appearing colon.

TABLE 4
Indications for Surgical Intervention in 17 Patients with Granulomatous Colitis

	17 Primary Definitive Operations		28 Later Definitive Operations
	Major Indication	Supplementary Indication	
	<i>No. Cases</i>		
Chronic disease.....	3	14	5
Exacerbation of disease.....	0	6	
Abdominal abscess and fistula.....	3		5
Abdominal mass.....	1		
Intestinal obstruction.....	2		7
Perirectal suppuration.....	3	2	8
Retarded development.....	1	2	1
Rectal hemorrhage.....	1		
Systemic complications.....	1	1	
Perforation.....	1		1
Hydronephrosis.....	1		1

TABLE 5
45 Definitive operations in 17 Patients with Granulomatous Colitis

Operations	Order of Definitive Procedure							Total No. Procedures
	1st	2nd	3rd	4th	5th	6th	7th	
	<i>No. of Cases</i>							
Ileocolostomy and resection.....	9	1	2	2	1			15
Ileocolostomy.....	5	1						6
Ileostomy, subtotal colectomy.....	2							2
Ileostomy.....	1	2	3			1		7
Subtotal colectomy.....		6						6
Abdomino-perineal resection.....		2	1	2			1	6
Ileo-ileostomy.....			1					1
Ileal resection.....			1		1			2
Total.....	17	12	8	4	2	1	1	45

TABLE 6
71 Operative Procedures in 17 Patients

No. operations....	1	2	3	4	5	6	7	8	9	10	11	12
No. cases.....	3	5	2			4	1		1			1

Average: 4.2 per patient.

TABLE 7
Extension of Disease Following Surgery in 17 Cases of Granulomatous Colitis

Primary Operation	No. Cases	Extension to Rectum					Rectum Resected (No. Cases)	Extension to Ileum			Further Surgery	
		No. Cases	Without Further Surgery	After Further Surgery	Before Primary Surgery	No. Cases		Without Further Surgery	After Further Surgery	Ileostomy	Ileal Resec- tion	
			No. Cases					No. Cases				No. Cases
Ileocolostomy.....	4*	2	1	1		2	2		2	1	2	
Ileocolostomy, sub- total colectomy...	10	6†	5	1		2	5	4	1	1	1	
Ileostomy, subtotal colectomy	3	2		1	1	2	1	1		1	1	
Total.....	17	10	6	3	1	6	8	5	3	3	4	

* 1 death

† 2 deaths

TABLE 8

Late Results and Recent Status of 25 Patients with Granulomatous Colitis

	No. Cases	Colon Resected	Rectum Resected	Died	Active Proctitis	Normal Rectum	Extension to Ileum	Asymptomatic for 5 Years
		No. Cases						
Non-operative...	8			1	0	7	0	3
Operative								
Ileostomy.....	7	7	6	1	1	—	3	1
Ileocolostomy...	10	8	—	2	4	4	5	2
Total	25	15	6	4	5	11	8	6

Mean follow-up 17 years (2 to 30).

TABLE 9

Relationship of Original Extent of Involvement Upon Clinical Status and Extension of Disease at Follow-Up

	No. Cases	Clinically Well 5 yrs. No. Cases	Recurrent Illness No. Cases	Died No. Cases	Spread of Disease	
					Proximal	Distal
					No. Cases	
Inflammatory disease confined to colon						
Nonoperative.....	1	1	0	0	0	0
Operative.....	5	2	3	0	4	5
Total.....	6	3 (50%)	3 (50%)			
Inflammatory disease of colon and ileum						
Nonoperative.....	7	2	5	1	0	0
Operative.....	12	2	10	3	9	7
Total.....	19	4 (21%)	15 (79%)			

Congenital Abnormalities of the Small Bowel*

JOHN E. MOSELEY, M.D., AND JACK G. RABINOWITZ, M.D.†

Congenital abnormalities of the small bowel are usually manifested in the neonatal period as intestinal obstruction. Congenital defects not causing significant neonatal obstruction may first become apparent in later infancy or childhood. Failure to recognize neonatal obstruction or undue delay in its surgical correction usually results in death of the infant.

The most important aids in the radiographic diagnosis of small bowel obstruction in the newborn are the supine, prone and erect survey films of the abdomen. Air, already present in the gastrointestinal tract, or air injected after aspiration of fluid, is all that is usually necessary for proper evaluation. Diagnostic criteria are based on the distribution and quantity of gas. Accurate interpretation of the findings requires an understanding of the normal intestinal gas pattern in newborn infants.

If there is no esophageal obstruction, air is usually present in the stomach immediately after birth (1). This is due partly to swallowing and apparently also partly to crying which results in inspiratory movements against a closed glottis with relaxation of the superior esophageal sphincter (2). Some gas can be seen in the small bowel within 5 to 30 minutes after birth and the entire small intestine may contain gas after three hours. Gas usually reaches the ascending colon between 3 and 4 hours after birth and the colon is outlined by gas in approximately 5 hours (3). A film of the infant's abdomen made after 24 hours of life will normally show gas distributed throughout the entire gastrointestinal tract (Fig 1). Generally the passage of gas through the intestinal tract is more rapid in the premature than in the mature infant.

In infancy it is usual for gas to be distributed throughout the entire gastrointestinal tract and the presence of gas and fluid levels in the small bowel under such circumstances is not abnormal. Usually the diffuse distribution of gas forms a polyhedral small bowel pattern which is characteristic (Fig 1). With increasing age and ambulation decreasing quantities of gas are seen in the small intestine and gradually the intestinal gas distribution approaches that seen in the older child and adult.

Occasionally the abdomen of the newborn is gasless or shows a significant paucity of gas several hours after birth. According to Singleton (3) this is sometimes the result of keeping the infant in a prone position during the interval between birth and the roentgen examination, but this appearance may be seen when there is respiratory depression as in the premature or brain-damaged infant. It may also be observed in infants born to mothers who have been heavily sedated or anesthetized during delivery. In recent years we have

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Fig. 1. Normal abdomen in infant approximately 24 hours old. Gas is distributed through entire small and large bowel and no abnormal distention is visualized. Small bowel demonstrates a typical polyhedral configuration.

observed the same phenomenon in newborn infants of mothers addicted to narcotics. In infants, diarrhea and dehydration also may result in a gasless or relatively gasless abdomen.

Without the benefit of clinical information and from a purely roentgen point of view a gasless abdomen in the neonate should suggest the possibility of an esophageal atresia without a fistula between the trachea and the lower esophageal segment. It must not be forgotten, however, that in an occasional case of small bowel obstruction fluid may displace the gas and, especially in

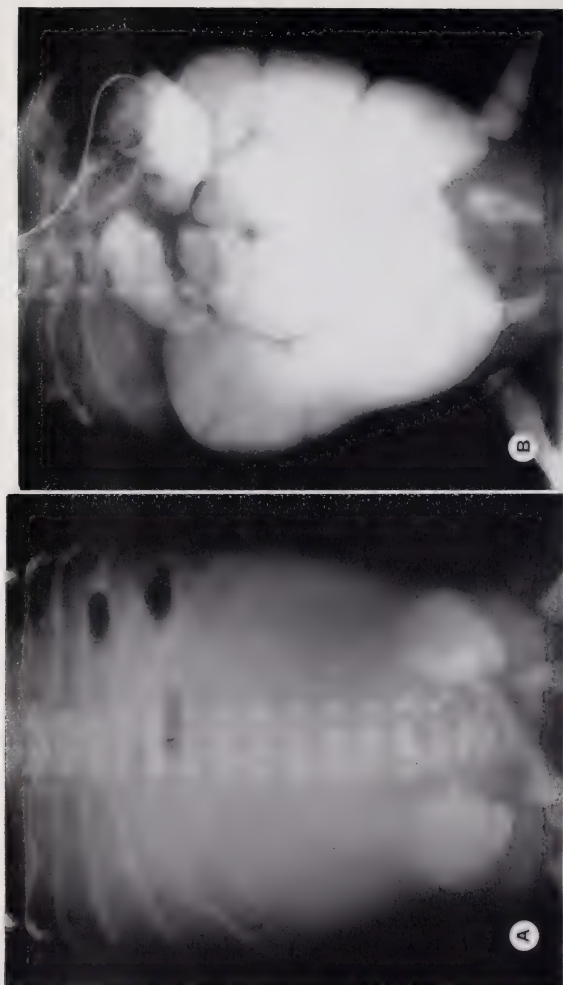


Fig. 2. Jejunal atresia in a 36 hour old infant who presented with vomiting and abdominal distention. A. The abdomen is relatively gasless, although there are collections of gas in the right upper quadrant within the stomach and proximal small bowel. Abdomen is distended indicating presence of fluid within the bowel or abdomen. This feature is compatible with small bowel obstruction in which the gas is almost completely replaced by fluid. B. Injection of opaque material demonstrates marked small bowel distention. Air injection would be equally diagnostic. A low jejunal atresia was diagnosed and confirmed.

the supine position, no gas may be demonstrable. In the erect position a small air fluid level may be noted in the stomach or in both stomach and small bowel (Fig 2). In such cases aspiration of gastric fluid and injection of an equal amount of air will usually outline the level of a high small bowel obstruction.

In high small bowel obstructions involving the duodenum or proximal jejunum it is the absence or marked decrease of intestinal gas distal to the gas filled proximal bowel and stomach which characterize the condition on survey films of the abdomen. When obstruction involves the lower small intestine dilated loops of bowel may present a confusing gas pattern and distinction between small and large bowel may be impossible. In infants distention of the small intestine usually results in loss of its fold pattern. The polyhedral or honeycomb gas pattern seen under normal conditions is no longer observed and in most cases multiple fluid levels are seen in the erect position. In those cases where the obstruction is low and the abdomen is filled with smoothly outlined loops of bowel it is generally necessary to perform a barium enema to determine the location and character of the colon. Rarely is it necessary to resort to the use of oral contrast material to outline the point of obstruction. The use of water soluble contrast media is not without risk because of their high osmolar activity and there is some clinical evidence to indicate that infants undergoing investigation with such media may succumb to a severe state of hypovolemia (4). The barium enema examination, on the other hand, is a strongly advised procedure in cases of suspected small bowel obstruction because it not only reveals the location of the colon but also makes possible the distinction between small intestinal obstruction and colonic obstructions such as meconium plug syndrome and Hirschsprung's disease. In addition, a malrotated colon suggests the presence of malrotation of the small bowel and mid-gut volvulus. In cases of complete low congenital small bowel obstruction such as atresia of the terminal ileum the barium enema will reveal a microcolon which results from failure of meconium to pass through the colon in intrauterine life. Low small bowel lesions usually result in colons of smaller calibre than those observed with higher lesions because in the latter instances the colon does act as a passageway for meconium formed below the obstructing lesion.

Duodenal Atresia and Stenosis

The most commonly encountered congenital obstructive lesions of the duodenum are those due to atresia, stenosis, annular pancreas, peritoneal band and volvulus. The symptoms of atresia occur within the first 24 hours of life, usually after the first feeding. Vomiting is the most prominent feature and since the atresia is most often distal to the ampulla of Vater the vomitus is usually bile stained. Abdominal distention may not be marked and it may be said that with high obstruction vomiting is more severe while with obstructions of the lower small bowel distention is more prominent. There is a fairly high incidence of hyperbilirubinemia with duodenal and jejunal atresia. Boggs

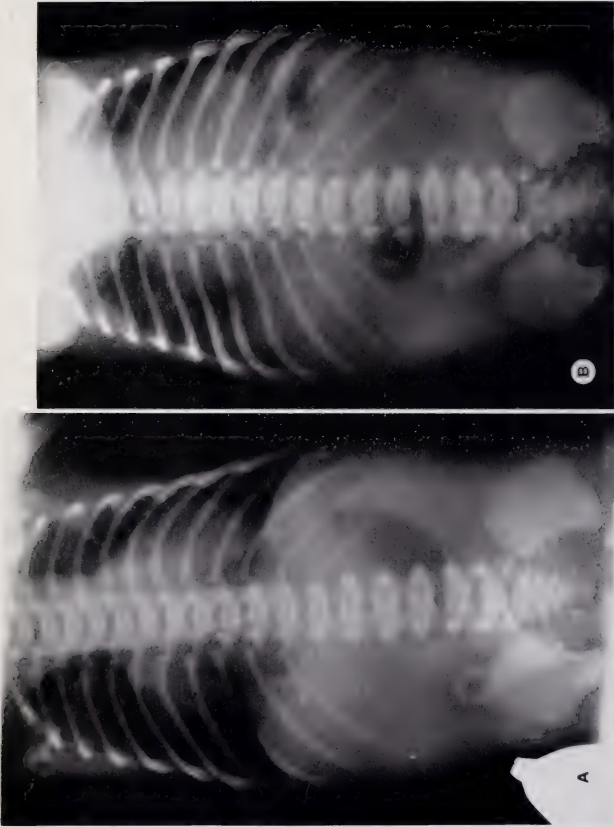


Fig. 3. Duodenal atresia and Down's Syndrome in a one day old baby girl who presented with vomiting. A. On a supine film of the abdomen air is present within the stomach. In addition there is cardiac enlargement associated with increased pulmonary vascular markings. Flaring of the iliac wings is also noted. B. Upright film of abdomen reveals a double bubble. The distended duodenal bulb is seen as a large air collection with an associated air fluid level in the right upper quadrant. Air in fundus of stomach represents the second part of the double bubble. In this case, demonstrates the importance of studying the chest and pelvis in addition to the abdomen.



Fig. 4. Duodenal atresia. A hugely distended stomach and duodenal bulb are noted. The large circular collection of air in right upper quadrant is the duodenal bulb through which the distal part of the antrum can be seen.

and Bishop (5) have found that 48 percent of 48 infants with these conditions developed excessive total serum bilirubin concentrations. The primary cause for this is as yet not clearly defined. An association between hyperbilirubinaemia and hypertrophic pyloric stenosis has also been uncovered. The frequent association between Down's syndrome and duodenal atresia and annular pancreas is also noteworthy. The incidence of this syndrome is greater with duodenal atresia where it occurs in about 30 percent of cases. The radiologist would be well advised, therefore, when viewing the survey films of an infant with high intestinal obstruction to study the bones for evidence of the skeletal manifestations of this chromosomal abnormality (Fig 3). There is no association between Down's syndrome and jejunal and ilial atresias.

Duodenal atresias are more commonly associated with other serious congenital anomalies than are the jejunal and ilial atresias, a fact which is re-

flected in the high mortality with these lesions and which may be related to a difference in pathogenesis. Currently there are two outstanding concepts regarding the pathogenesis of intestinal atresias. It has been confirmed by several investigations that development of the human duodenum passes through a solid stage in some embryos due to mucosal proliferation. This proliferation leads to obliteration of the lumen in the 5th and 6th week. The lumen is reformed by vacuoles which coalesce and reestablish the lumen by the 8th week of intrauterine life (6). Complete or partial failure of vacuolation and recanalization could result in atresia or stenosis. It is also considered that interruption of the blood supply to a bowel segment with resulting infarction may cause disintegration and eventual disappearance of the affected segment (7). The development of the jejunum, ileum and colon only rarely passes through a solid stage and it is tentatively considered that while some cases of duodenal atresia may be due to failure of recanalization (Tandler's theory) atresias of the jejunum, ileum and colon are more likely due to vascular accidents occurring later in fetal life.

Radiographically duodenal atresia is characterized by gaseous distention of the stomach and that portion of the duodenum proximal to the site of atresia and absence of gas distally. When atresia involves the second portion of the duodenum a characteristic "double bubble" sign is formed by gas in the fundus of the stomach and in the duodenal bulb with a total absence of gas in any other portion of the abdomen (Fig 3B, 4). Two large bubbles of this type are seen with duodenal atresia and with some cases of annular pancreas which are associated with duodenal atresia (Fig 5). Obstructions of the duodenum by stenosis, peritoneal bands, volvulus or annular pancreas without atresia usually do not produce such considerable dilatation of the duodenal bulb.

Stenosis implies partial obliteration of the intestinal lumen. While multiple areas of atresia are not uncommon (15 to 25%) multiple areas of involvement by stenosis are relatively rare. Clinical distinction between stenosis and atresia is based on the degree of obstruction. Severe stenosis may present as early as atresia and the obstruction may be marked (Fig 6). When stenosis is less severe, clinical symptoms are milder and may, in fact, be delayed for days or weeks or may be intermittent. In some instances the clinical picture may resemble that seen with milk allergy or other feeding problems. When the stenosis is minimal there may be no symptomatology until much later in life.

Radiographically duodenal stenosis, unlike atresia, results in the appearance of an incomplete obstruction. The stomach and duodenal bulb may show variable degrees of distention but characteristically some gas will be seen distal to the dilated proximal duodenum (Fig 7). More often than not much of the small bowel will contain collections of gas without distention.

Annular Pancreas

Annular pancreas is a band of pancreatic tissue which arises from the head of the pancreas and forms a partial or complete ring around the second por-

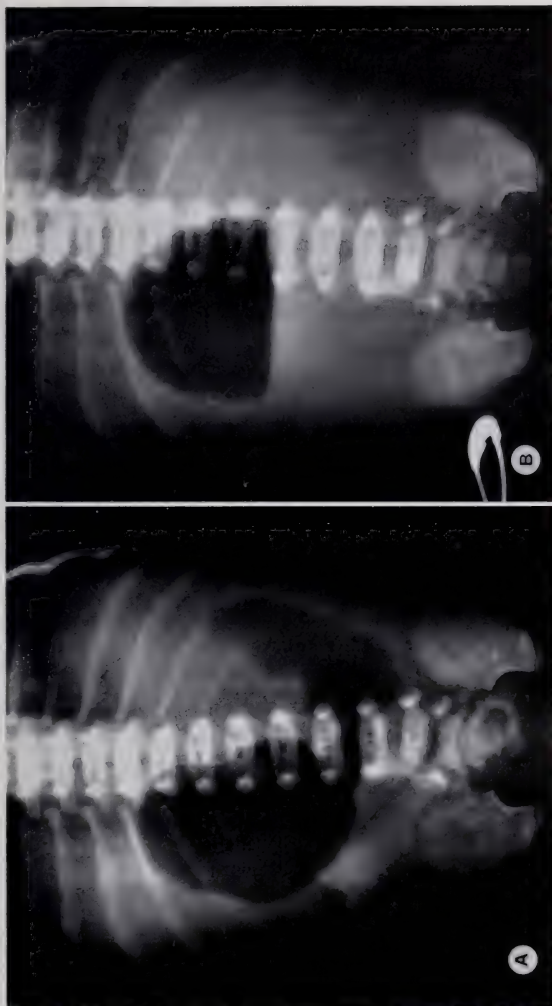


Fig. 5. Annular pancreas and associated duodenal atresia in a newborn. A. Supine film demonstrates marked distention of the duodenal bulb within right upper quadrant as well as air within stomach. B. The huge duodenum with an associated air fluid level is again seen on the upright film. The stomach contains a considerable amount of fluid and only a small air fluid level is noted in left upper quadrant.



Fig. 6. Severe duodenal stenosis in a newborn. Stomach and duodenum are dilated and contain residual opaque material from a previous study. No gas is seen distal to the distended duodenum and differentiation between duodenal atresia and stenosis in this situation would be impossible.

tion of the duodenum. When the ring is incomplete it takes the form of two arms extending from the head of the pancreas partially engulfing the duodenum but leaving a space on its ventral surface which is filled with loose fibrous tissue (8). When complete it may be associated with an underlying duodenal atresia.

The clinical manifestations of annular pancreas depend upon the degree to which the lesion obstructs the duodenum. Complete obstructions present with the same clinical and roentgenographic appearance as duodenal atresia. With incomplete obstructions symptoms tend to be delayed until later in childhood or even until adulthood and usually consist of intermittent nausea, vomiting and epigastric pain. When there is no obstruction, symptoms referable to annular pancreas may be absent throughout life, the lesion being discovered only incidentally at autopsy.



Fig. 7. Duodenal stenosis. Dilated stomach and duodenum are outlined by opaque material. Distal to the obstructed duodenum small air collections are present within both small and large bowel. This feature indicates the presence of an incomplete duodenal obstruction compatible with stenosis, annular pancreas, or an extrinsic process.

The roentgen findings in annular pancreas are related to the degree of obstruction. When the obstruction is complete or associated with atresia there is considerable distention of the duodenal bulb and stomach which present as the "double bubble" identical to that described in duodenal atresia (Fig 5). In some cases, however, the obstruction is almost but not quite complete. In these instances small bubbles of gas may be seen distal to the site of obstruction. While this appearance excludes duodenal atresia it cannot be differentiated from partial obstruction due to stenosis or an extrinsic process. In these circumstances a barium enema should be performed to exclude malrotation as a cause of the obstruction. While there are no pathognomonic roentgen signs of annular pancreas this condition should be included in the differential diagnosis of all complete or partial obstructions of the second portion of the duodenum. In those cases in which the duodenal obstruction is mild permitting passage of significant amounts of gas to outline the small bowel fur-

ther examination with the aid of contrast material is justified. In such examinations annular pancreas is usually seen as a concentric narrowing or a smooth compression of the right side of the second portion of the duodenum.

Malrotation

In order to appreciate the effects of malrotation it is important to understand the normal rotation of the intestines which occurs during fetal life. The superior mesenteric artery is the main fulcrum around which the intestines rotate. Initially the intestinal tract is a straight tube lying in front of the superior mesenteric artery. As the small bowel, right colon and part of the transverse colon extend outside of the abdomen into the cord, the duodenum begins to curve downward and to the right of the artery. At about the 25 mm stage, the duodenum lies beneath the artery completing a rotation of 180 degrees. At approximately the 10th week or the 40 mm stage the intestines begin their return to the abdomen. The small intestines migrate inward initially and push the duodenum and jejunum to the left completing a 270 degree turn around the vessel. The rotation corresponds to a 270 degree turn in a counterclockwise direction. The right colon returns last to the abdomen and is therefore located on the left side of the artery. The cecum then continues to migrate above and anterior to the vessel in a counterclockwise direction to attain its normal position on the right side of the superior mesenteric artery. Completing this process, it similarly has undergone a 270 degree turn.

Any alteration of the normal sequence of rotation can result in some form of non or malrotation. The more frequent abnormalities are worth mentioning. Incomplete rotation of the colon usually terminates with the cecum above the superior mesenteric artery. As a result of this incomplete process, the usual peritoneal attachment of the right colon forms bands which extend from the right colon across the duodenum to the right upper quadrant, a situation predisposing to duodenal obstruction.

Failure of the jejunum to rotate normally under the superior mesenteric artery results in an abnormal attachment of the mesentery of the small bowel to the posterior wall. Consequently the only line of attachment is a small narrow area around the superior mesenteric artery. The small bowel is then exceedingly mobile and volvulus occurs easily. If and when the duodenojejunal loop fails to pass underneath the artery and passes anteriorly instead, it becomes adherent to the mesentery at a lower level. Bands and adhesions form across the proximal portions of the jejunum with resulting obstruction. An unusual and rare form of rotation is the passage of the cecum underneath the artery. This is termed reversed rotation. Other rare manifestations related to

Fig. 8. Non-rotation of the mid-gut.

A. Gastrointestinal series demonstrates the small bowel to be lying completely within the right side of the abdomen. B. Barium enema performed on the same patient reveals the entire colon located on the left side of the abdomen. Cecum and terminal ileum are situated within the left upper quadrant.

This child had recurrent bouts of abdominal pain and, shortly after the above studies were performed, entered the hospital in acute distress. A mid-gut volvulus was reduced at surgery.

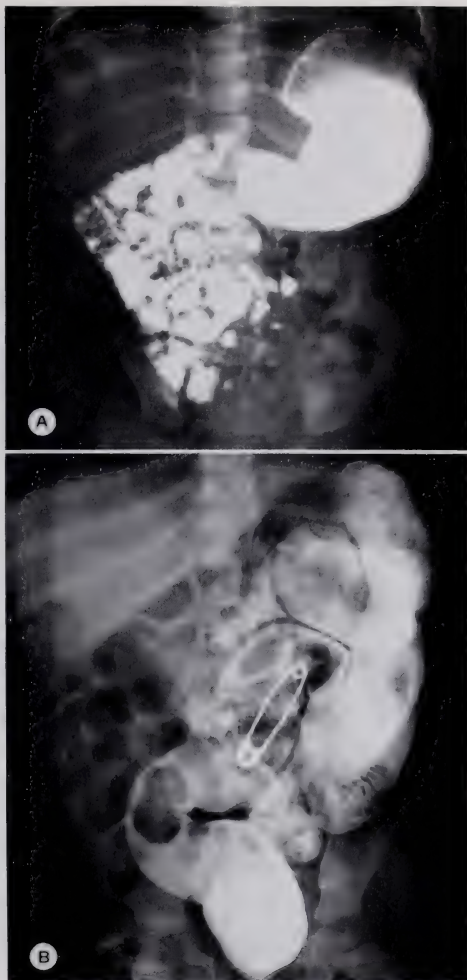
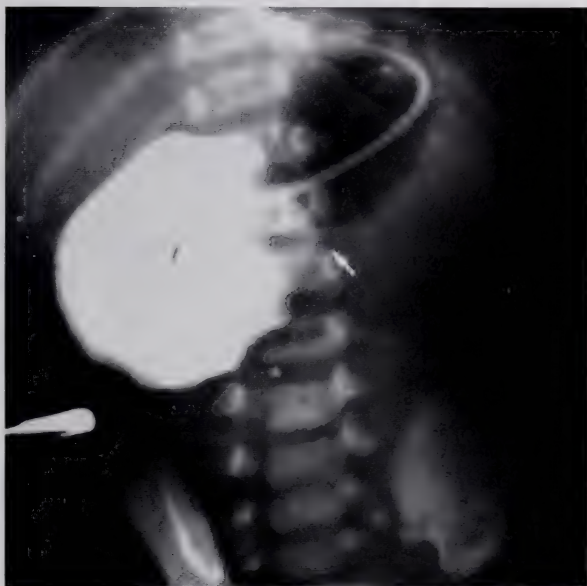




Fig. 9. Malrotation and mid-gut volvulus in a three day old infant who was vomiting bile-stained material. A. Supine film of abdomen reveals a dilated stomach and duodenal bulb with no visible air distal to this area. B. On the upright film of the abdomen a large air fluid level is present within the stomach with minimal air noted within the duodenal bulb. The above findings are compatible with a duodenal obstruction and the differentiation between duodenal atresia and mid-gut volvulus may be difficult. However, the duodenum is only minimally dilated; a feature not associated with atresia.

Fig. 9C. With the insertion of opaque material the obstruction is demonstrated at the level of the ligament of Treitz (arrow). At surgery malrotation with minimal volvulus was present and the third portion of the duodenum was obstructed by peritoneal bands.



rotation are the presence of right and left paraduodenal hernias. These hernias are rarely encountered in childhood and represent imprisonment of the small bowel within the mesentery of the large bowel.

As summarized by Singleton (9) variations in the rotation and fixation of the intestines may result in numerous anomalies, the radiologically most important of which are non-rotation, malrotation, reversed rotation and normal rotation with inadequate mesenteric-peritoneal fusion. Volvulus of the mid-gut or obstruction due to peritoneal bands may complicate any of these varieties of abnormal rotation or fixation. It will aid in the roentgen evaluation of these conditions if one keeps in mind the final anatomical pattern associated with these anomalies. In non-rotation the mid-gut returns to the peritoneal cavity without completing its rotation around the superior mesenteric artery and comes to lie in the right abdomen and the colon and cecum return to and remain in the left abdomen (Fig 8). In malrotation (incomplete rotation) the prearterial segment is usually in a normal position but the key to the degree of malrotation is seen in the position of the cecum. This may be in the left abdomen, the epigastrium or high on the right side. In some cases only an abnormally mobile cecum may be noted. In reversed rotation the positions of the duodenum and colon are reversed, i.e., the duodenum overlies the colon and is separated from it by the superior mesenteric artery.

Clinical manifestations resulting from non-rotation or malrotation of the intestinal tract are due to complete, partial or intermittent obstructions associated with peritoneal bands, mid-gut volvulus or both. Although the second portion of the duodenum or the more distal parts of the small bowel may be affected the third portion of the duodenum is usually the site of the obstruction. In the neonatal period the obstruction is usually complete or at least severe. The predominant symptom is vomiting. Should the obstruction involve a site lower in the small bowel significant degrees of abdominal distention will be noted. The more usual involvement of the third portion of the duodenum is not associated with distention or is associated with distention of the upper abdomen only. Vomiting may occur on the first day of life but in incomplete obstructions it may be delayed for a week or so or even later in childhood when it may be intermittent in character simulating cyclic vomiting or an allergic disorder. As a matter of fact, it should be noted that in later childhood malrotation may give rise to symptoms and signs similar to those of celiac disease. In such cases torsion of the small bowel is considered to result in partial obstruction of the superior mesenteric vein with resulting intramural edema, congestion and malabsorption. It is also possible that twists in the bowel may result in chronic or intermittent obstructions at the terminal ileum. At any rate these children do present with chronic or intermittent abdominal distention, signs of malabsorption and constipation or diarrhea.

In the neonatal period complete obstruction of the duodenum due to bands and/or mid-gut volvulus present roentgen findings similar to those of other complete duodenal occlusions (Fig 9). It is more likely, however, that obstructions due to these lesions will be located in the third portion of the duodenum and while there is dilation of the proximal duodenum the degree of dila-



Fig. 10. Malrotation and mid-gut volvulus in a six week old infant with recent onset of bile-stained vomiting.

Stomach and duodenum are distended. The obstructed distal third of duodenum (arrow) is visualized through the gastric antrum. No air is seen distally.

Findings at surgery were malrotation with mid-gut volvulus. In addition a peritoneal band extended across and obstructed the duodenum.

tation of the duodenal bulb seen in duodenal atresia is usually not present in obstructions due to malrotation anomalies (Fig 9, 10). If the infant's condition warrants it the most important diagnostic procedure following the survey films is a barium enema. The combination of duodenal obstruction and evidence on the enema films of malposition of the cecum is diagnostic of malrotation with peritoneal bands and/or mid-gut volvulus.

Where malrotation has resulted in an incomplete obstruction moderate dilatation of the proximal duodenum will be associated with variable amounts of gas in the lower small bowel. The appearance will be similar to that of duodenal stenosis. The site of obstruction in malrotation with mid-gut volvulus is not always at the third portion of the duodenum, however, and may occur in the jejunum or the ileum (Fig 11). Barium enema studies will facilitate diagnosis by indicating an abnormal position of the cecum consistent with some form of malrotation. Rarely, malrotation and mid-gut volvulus will present as duodenal obstruction associated with fluid filled loops of small bowel (pseudotumor) (Fig 12).

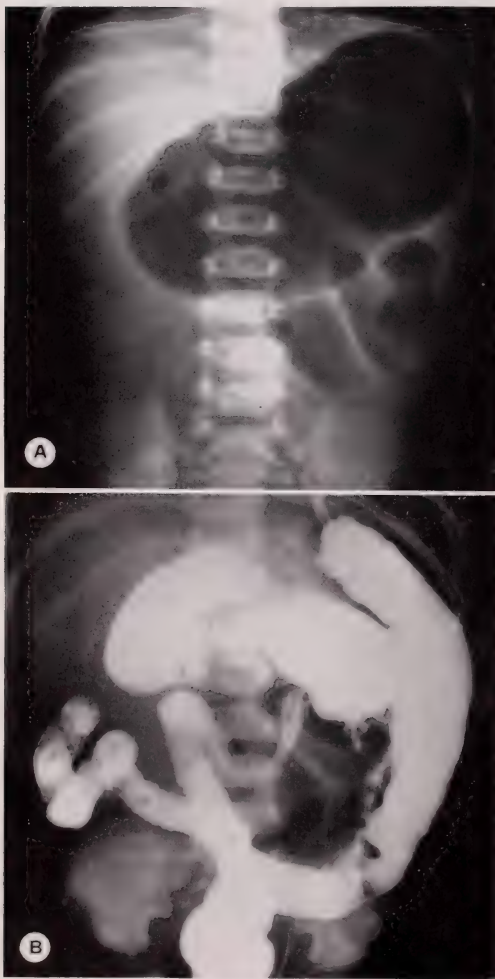
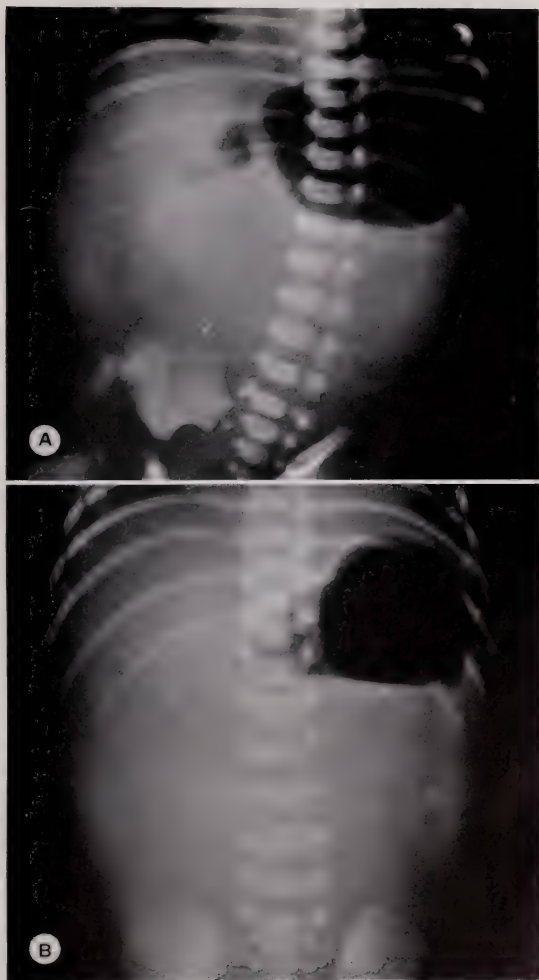


Fig. 11. Malrotation and mid-gut volvulus in a four day old infant who on the first day of life passed a large bloody meconium stool and began to vomit shortly afterward. A. Supine film of abdomen reveals a distended stomach, as well as some dilated loops of small bowel within left upper quadrant. These findings suggest a small bowel obstruction most likely jejunal. B. On barium enema examination the colon is completely located within the left abdomen indicating the presence of a malrotation and probable mid-gut volvulus. These findings were confirmed at surgery. (Courtesy of Dr. H. Grossman, New York, N. Y.)

Fig. 12. Malrotation, mid-gut volvulus, and meconium peritonitis in a newborn who presented with abdominal distention and vomiting. A. Stomach and duodenum are moderately dilated and only a portion of the duodenal sweep is visualized. No air is seen distally. However, there is a soft tissue mass in the right upper quadrant displacing the duodenal sweep. The mass represents fluid filled infarcted small bowel. B. On the upright film an air fluid level is seen within the stomach. In addition mottled calcifications indicating meconium peritonitis are present in left part of abdomen. Findings at surgery were malrotation, mid-gut volvulus and meconium peritonitis.



Jejunioileal atresia and stenosis

Atresia and stenosis of the jejunum and ileum are less often associated with other important congenital anomalies than are the duodenal occlusions and they have no particular relation to the occurrence of Down's syndrome. Louw (10) found the most serious abnormalities associated with jejunioileal occlusions to be meconium peritonitis and omphalocele. As with duodenal occlusion, hyperbilirubinemia is often found associated with obstructing jejunal lesions. Louw (10) found 5 of his 17 cases to be deeply jaundiced, 3 of them requiring exchange transfusions.

High jejunal lesions may present a clinical picture similar to that of duodenal obstruction but the lower the obstruction is in the small bowel the more prominent is the abdominal distention and the less frequent is the vomiting. Delay in the diagnosis of jejunal or ileal atresias and severe stenosis is particularly dangerous because increasing distention of the bowel wall leads to vascular changes and eventual perforation.

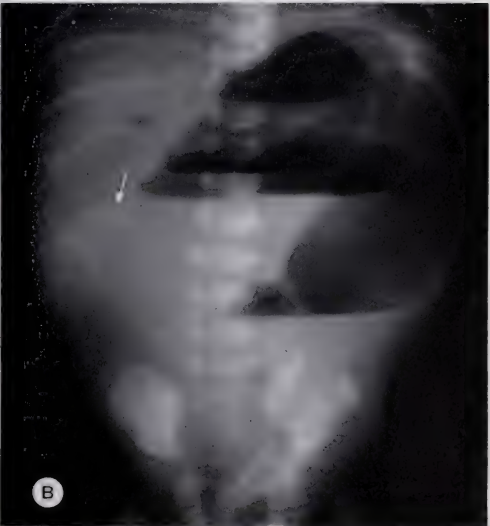
Atresia, which is more commonly encountered than stenosis, presents radiographically as a complete obstruction of the small bowel with distention of the small intestine proximal to the site of the obstruction (Fig 13, 14). There is no gas demonstrable in the large bowel or rectum. When the obstruction is in the jejunum the gas-filled loops of intestine tend to be localized to the upper abdomen in the erect position. Occlusions involving the more distal portions of the small bowel frequently become more difficult diagnostic problems because a greater length of bowel becomes distended and the infant abdomen is crowded with gas-filled loops with no characteristic markings or position making differentiation between small bowel and colon practically impossible on the survey films. In this circumstance a barium enema examination will indicate the position and condition of the colon making it possible to differentiate between small bowel and colonic obstruction. As noted above distal small bowel atresia is associated with microcolon since there has been passage of little or no meconium through the colon (Fig 15). Higher levels of atresia are associated with larger colons because of the passage of quantities of meconium formed below the site of obstruction. Small bowel stenosis presents as an incomplete obstruction and variable quantities of gas will be seen distal to the point of obstruction (Fig 16).

Duplications

Duplications of the intestinal tract may cause complete or partial obstruction of the small bowel. While this usually does not occur until late infancy or early childhood it may develop in early infancy. Duplications may arise from any portion of the alimentary tract from the tongue to the anus; but these congenital anomalies are most common in the ileum and esophagus. Gross et al (11) found that of 39 duplications involving the small intestine the distribution was as follows: 4 in the duodenum, 4 in the jejunum, 20 in the ileum and 8 at the ileocecal junction. Three others arising from the duodenum or jejunum extended as a tubular structure through the diaphragm into the thorax.

Fig. 13. Jejunal atresia and meconium peritonitis in a two day old infant with vomiting.

The small bowel is markedly dilated. Valvulae conniventes are still detected within a large loop of jejunum located in mid-portion of abdomen. In the right upper quadrant are collections of calcification (arrow) indicating presence of meconium peritonitis. A. Upright film of abdomen demonstrates huge air fluid levels and peritoneal calcifications (arrow). At surgery, jejunal atresia was present with a small perforation just proximal to the atresia.



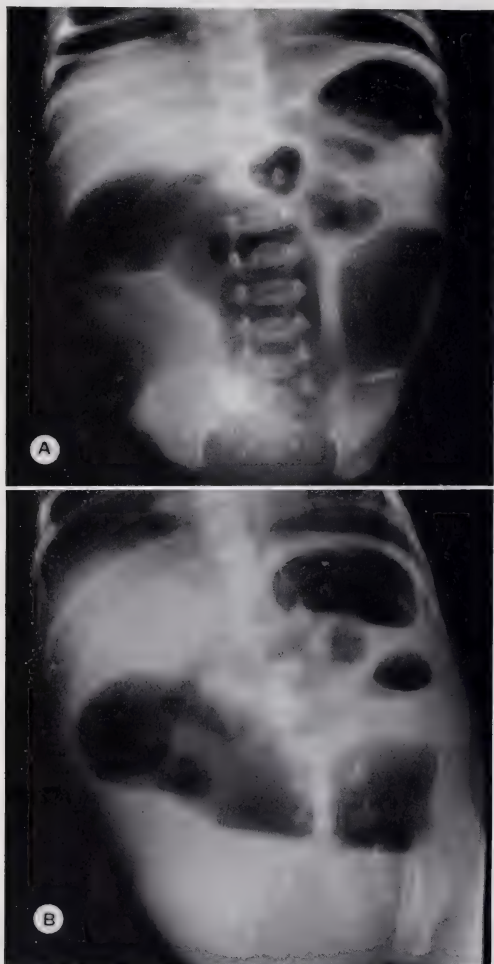


Fig. 14. Jejunal atresia. A. Distended loops of small bowel are noted predominantly in the upper abdomen. B. Upright film, same patient, demonstrates air fluid levels within the small bowel. Although no characteristic bowel markings are maintained, the predominant location within the upper abdomen and the limited number of distended loops suggest jejunal atresia.



Fig. 15. Iliac atresia, malrotation, and volvulus in a one day old infant presenting with abdominal distention. The original study of the abdomen demonstrated distended small bowel loops.

Barium enema reveals a microcolon extending from the sigmoid to the cecum which is located in the right upper quadrant. There are also dilated small bowel loops and a mass is present in the right lower quadrant.

Iliac atresia and malrotation were diagnosed by the presence of a microcolon and an abnormally located cecum. A mass in right lower quadrant suggested an associated volvulus. All findings were confirmed at surgical exploration.

Duplications are usually spherical or tubular in shape, have a well developed smooth muscle layer and are lined with a mucous membrane. The type of mucosa is not always similar to that of the adjacent intestine and on occasion there may be 2 or 3 different types of mucosa in a single structure.

It is considered that duplications arise during the stage of recanalization of the intestinal tract. The solid cord of epithelial cells which have obliterated the lumen are recanalized by vacuoles which coalesce to reestablish a lumen. If one vacuole fails to coalesce with the reformed lumen it may persist as a duplication.

Duplications of the small bowel usually present clinically as partial or complete intestinal obstruction. This results from compression of a segment of



Fig. 16. Jejunal stenosis. Jejunum is markedly distended although gas is present distal to the dilated bowel. The features indicate an incomplete small bowel obstruction. At surgery the obstruction was caused by a membrane with a small pinpoint opening.

Fig. 17. Ileocecal duplication in a newborn. A. A large mass is present within the right lower quadrant (arrows) outlined along its lateral and inferior margins by air within the bowel. Small bowel is moderately dilated although gas is seen within rectum. B. Barium enema study again outlines the mass in right lower quadrant (arrow).



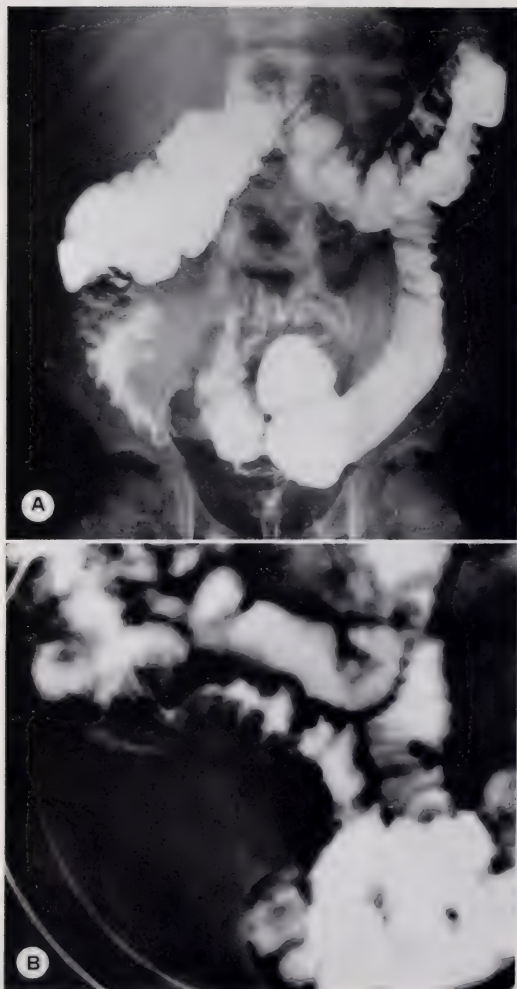


Fig. 18. Ileal duplication in a young boy who presented with right lower quadrant pain of one month duration. A. Mass is seen displacing medial part of cecum as well as the adjacent small bowel. B. Spot film of terminal ileum obtained during a small bowel study reveals the extrinsic nature of the mass as well as its mobility. The mucosa of the terminal ileum is altered but not destroyed or infiltrated. (Courtesy of Dr. H. Grossman, New York, N. Y.)

intestine by a noncommunicating adjacent duplication which has become distended by the accumulation of secretions within it. In some instances the duplication may obstruct by intussusception or by torsion with small bowel volvulus. Pain may result from over-distention of the duplication. When there is a lining of gastric mucosa and communication between the duplication and the adjacent intestine, pain may result from peptic ulceration within the duplication or the adjacent communicating bowel segment. Bleeding is associated with ulceration or with interference of the vascular supply of the bowel by the distended duplication.

Duplications are only rarely filled by barium studies and can be appreci-

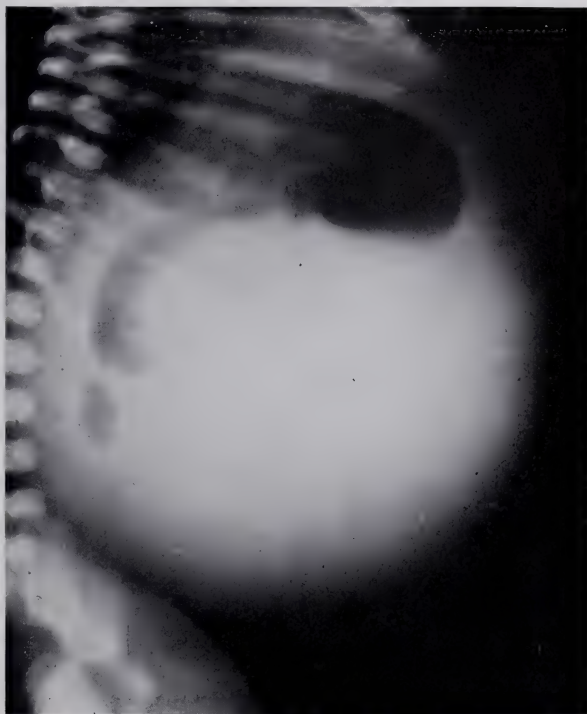


Fig. 19. Pseudocyst, meconium ileus. Lateral film of abdomen in a newborn with meconium ileus demonstrates huge cystic mass. Surgical exploration revealed this to be necrotic intestine filled with meconium. (Courtesy of Dr. H. Grossman, New York, N. Y.)



Fig. 20. Meconium ileus. A. Small bowel is markedly dilated. The small bowel on the left is considerably more dilated than that located on the right. A ground glass appearance due to the presence of meconium within the bowel is also observed on this side. Associated with this are multiple bubbles of air of variable sizes. B. Upright film of same patient demonstrates poorly defined and irregular air fluid levels. Air bubbles are still apparent since most of the air still remains adherent to the meconium.

ated on survey films only if they are quite large (Fig 17). Should a communicating duplication in the distal small bowel be visualized with barium its radiographic differentiation from Meckel's diverticulum would likely not be possible. The usual radiographic features of duplications are those of partial or complete small bowel obstruction. These may be at any level of the bowel although they are most commonly in the ileum and at the ileocecal region. Barium studies may reveal displacement of the adjacent bowel by a sharply defined extrinsic mass (Fig 17, 18). The intestinal mucosa will appear stretched with no demonstrable ulcerations. If a duplication is the cause of intussusception, it will be difficult to differentiate this from other mass lesions.

Duplications which arise in the small bowel and extend through the diaphragm into the thorax appear as spherical or tubular soft tissue densities in the posterior mediastinum. They are usually associated with anomalies of the lower cervical or upper dorsal spine. Gross found that in all such lesions there was communication with the intestine at the site of origin of the duplication. In some cases the anomalous structure may be coiled upon itself in the thorax presenting a radiographic appearance difficult to distinguish from diaphragmatic hernia. The coexistence of a duplication extending into the thorax with a diaphragmatic hernia has been reported (11, 12).

Meconium Ileus

Meconium ileus is a common cause of intestinal obstruction in the newborn period. It is one of the protean manifestations of cystic fibrosis (mucoviscidosis) and occurs in approximately 20 per cent of all patients with that disorder. In meconium ileus the intestine is obstructed by abnormal meconium which becomes inspissated in the distal ileum. For some time it was considered that this abnormal meconium was the result of deficient enzyme production due to fibrosis of the pancreas. Recent pathological studies (13), however, indicate that altered small intestinal glands are primarily responsible for the development of meconium ileus and that pancreatic lesions are of secondary, if any, importance in the pathogenesis of this condition.

Introduction of new surgical techniques has increased the surgical survival rate (50%) in uncomplicated cases but meconium ileus is frequently accompanied by the intraabdominal complications of volvulus, gangrene, atresia and perforation. Atresia or volvulus without gangrene or peritonitis does not appear to alter the survival rate significantly but perforation, peritonitis and gangrene are ominous developments which gravely affect the survival prognosis (14). These secondary complications unfortunately are quite common and occur when the grossly distended meconium-filled loops twist upon themselves. In some cases vascular compromise leads to gangrene which in turn may progress to necrosis and perforation. At times there may be formation of a cystic mass of necrotic intestine containing fluid meconium. Santulli (15) has referred to this as a "pseudoecyst" (Fig 19). In meconium ileus atresias are considered to be the result of volvulus and of "inflammation and fibrosis" (14).

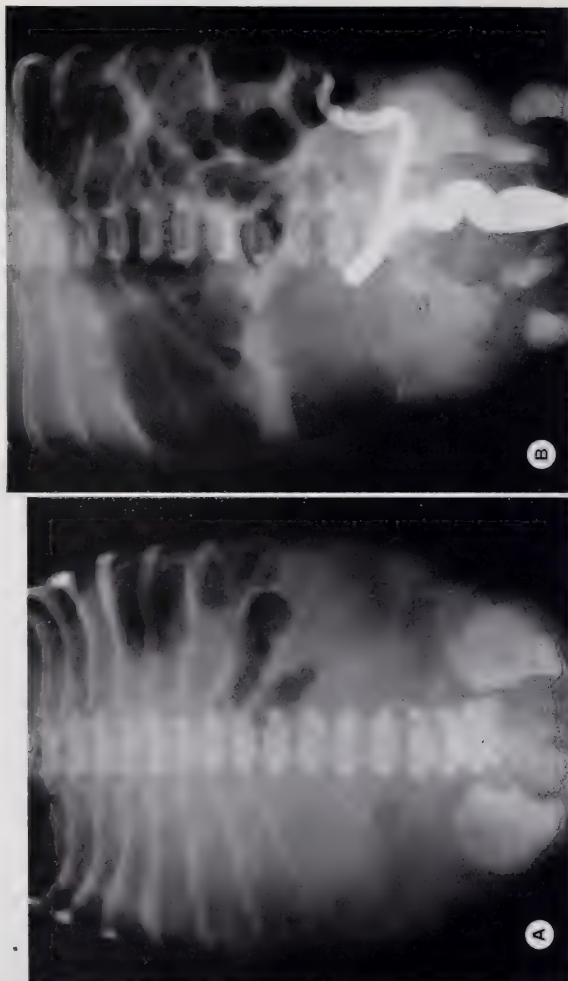


Fig. 21. Meconium ileus. A. Supine film of abdomen taken during the first day of life shows marked abdominal distention and discrepancy in small bowel distention. Within the left upper quadrant some dilated loops of small bowel are noted and little gas is present on the right side. B. Barium enema was performed the following day and demonstrates a typical microcolon. Also at this time there has been marked increase in small bowel distention. A ground glass appearance is observed within the right lower quadrant.

Although the clinical picture is essentially that of any neonatal low small bowel obstruction there are some suggestive features which may be noted. The abdomen is distended and hard. Rubbery loops of bowel which pit on pressure may be seen or palpated through the abdominal wall and rectal examination usually reveals an unusually small anus and rectum. About one-third of the patients will have a family history of cystic fibrosis or meconium ileus.

In some cases the radiographic appearance is indistinguishable from low small bowel obstructions due to other causes. In many cases, however, there are roentgen features which provide reliable clues to the correct diagnosis. Characteristically in many cases the gas-filled loops of small bowel may show a significant variability in size. Some may be considerably distended while others are only moderately dilated or practically normal in calibre (Fig 20). Neuhauser (16) first called attention to a ground-glass or soap-bubble pattern of the meconium in the bowel as seen on the survey film (Fig 20). This characteristic pattern is considered to be due to a mixture of air with thick inspissated meconium. While this soap-bubble pattern of meconium in the obstructed small bowel of a neonate should strongly suggest meconium ileus the same pattern occasionally may be seen in patients with ileal atresia or with aganglionic involvement of the terminal ileum. Another roentgen feature of some cases is the absence of fluid levels in the erect position (17) presumably due to the viscosity of the intestinal contents and the inhibition of intestinal secretion by the adherence of viscid meconium to the bowel wall. Absence of fluid levels in the erect position is not a feature of all cases, however and the presence of fluid levels does not necessarily mitigate against the diagnosis. The lack of fluid levels on the other hand is a strong clue favoring meconium ileus. When present, fluid levels tend to form slowly with change in the infant's position. In some cases a huge mass filling much of the abdomen and representing a large pseudocyst may be seen (Fig 19).

As with other low small bowel obstructions differentiation between small and large bowel may be impossible and a barium enema will reveal the position and character of the colon. In meconium ileus, the colon is usually very small in calibre (microcolon) as there has not been passage of meconium through it. (Fig 21). Although small or hypoplastic colons may be demonstrated in other forms of small bowel obstruction Singleton (9) has found that the smallest colons are seen with meconium ileus.

Complicating volvulus or atresia is usually first appreciated at surgery. Peritoneal calcifications indicative of prenatal meconium peritonitis may be noted especially localized around the peripheral regions of the peritoneal cavity. Calcifications may also be seen in the bowel wall. Associated congenital anomalies are relatively rare in meconium ileus (14).

Meconium Ileus Equivalent

Meconium ileus equivalent may occur in older infants and children and has been reported in patients ranging in age from 7 months to 15 years. The clinical features of this condition are those of mechanical intestinal obstruc-

tion occurring in a child known to have cystic fibrosis of the pancreas. Frequently the meconium ileus equivalent has been associated with inadequate dosage, cessation, or omission of pancreatic enzymes in treatment. Cordonnier and Izant (18) have called attention to certain aids in the diagnosis of this condition which must be differentiated from other forms of intestinal obstruction, particularly intussusception and postoperative adhesions. Often a soft, indentable mass of impacted material in the intestine can be palpated through the abdomen or rectum. Radiographically the flat film of the abdomen may show the cecum and ascending colon and the distal ileum to be filled with a soap bubble pattern of intestinal content similar to the soap bubble pattern of meconium in meconium ileus of the neonate. A contrast enema, preferably with a water soluble contrast medium, will sometimes demonstrate the intraluminal nature of the obstruction and the dilated proximal intestine and will make possible the exclusion of an intussusception.

Meconium Peritonitis

Meconium peritonitis is a non-bacterial, chemical peritonitis resulting from a perforation of the gastrointestinal tract during intrauterine or early neonatal life. Should the perforation remain patent after birth a secondary bacterial peritonitis results. In some cases no sign of perforation can be found at operation, indicating that perforation during intrauterine life was sealed off before birth. Meconium peritonitis is usually due to an intestinal obstruction resulting from thick, inspissated meconium in patients with fibrocystic disease of the pancreas or to intestinal atresia (Fig 13), and in some cases to a combination of both. Less commonly the condition may result from intestinal stenosis, volvulus (Fig 12), bands or rupture of a Meckel's diverticulum. In those infants who do not present with associated meconium ileus, the prognosis is more favorable providing the condition is diagnosed and treated prior to the onset of superimposed bacterial infection.

When the perforation has occurred in utero without an associated obstruction and with sealing of the defect before birth, the patients are asymptomatic and the disease is discovered fortuitously on films of the abdomen made for some unrelated reason. In general, however, meconium peritonitis is associated with an intestinal obstruction. Abdominal distention, vomiting, and obstipation are the usual clinical features. In some cases there may be variable degrees of pneumoperitoneum.

The roentgen diagnosis of meconium peritonitis is based on the identification of calcium within the peritoneal cavity on abdominal roentgenograms. Meconium in contact with the peritoneal fluid shows a marked propensity to calcify and calcification may occur in some cases as early as 24 hours after extrusion of the meconium into the peritoneal cavity. The intraabdominal calcium deposits may occur as a single cluster (Fig 13), a few small scattered clusters or as long linear calcium shadows which tend to be localized to the periphery of the abdomen (Fig 22). These lie on the peritoneal surface and are seen to be situated anteriorly or posteriorly in the lateral projection or at



Fig. 22. Meconium peritonitis in a newborn presenting with marked distention and scrotal swelling. There is very little gas distributed throughout the small bowel. Plaques and linear strands of calcification outline the abdominal flanks. In addition the scrotal sac is distended and there is a linear calcification within (arrow).

the flank in the antero-posterior projection. On occasion calcium deposits may be seen within the scrotal sac, extruded meconium having spilled into the scrotum through the communication between the peritoneal cavity and the processus vaginalis (Fig 22).

Although the calcific meconium salts in meconium peritonitis are easily



Fig. 23. Meconium peritonitis and ileal atresia. Lateral film of abdomen demonstrates intramural calcification within a loop of ileum. Somewhat superior to this area is a mottled collection of calcification. Small bowel is distended proximally indicating ileal atresia.

identified when they lie peripherally or in the serotal sac, it may be difficult to differentiate calcifications on the serosa of the bowel from intraluminal or intramural calcification (Fig 23). Intraluminal calcifications within inspissated meconium may occur in association with obstructions. The calcification in these instances is likely to appear as multiple rounded densities or, occasionally, as concentric rings in contrast to the cluster-like plaques or peripheral calcium lines of meconium peritonitis. Intraluminal calcifications, however, may also appear in a linear arrangement in which case their location is suggested by their more central position in the abdomen as seen in the AP and lateral projections.

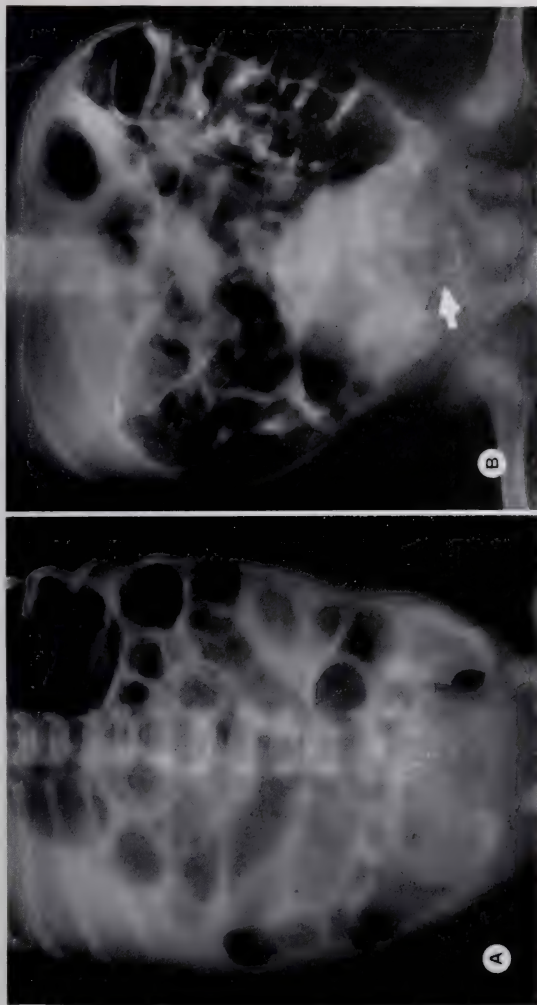


Fig. 24. Hirschsprung's Disease. A. The abdomen is distended with dilated loops of bowel. Differentiation between small and large bowel in this instance is impossible. B. A minimal amount of contrast material was inserted into the rectum and a transitional zone was observed fluoroscopically. (Unfortunately the material was evacuated prior to the exposure of the above film.) The distal sigmoid and rectum are narrow in comparison to the proximal dilated colon. Hirschsprung's disease was confirmed by rectal biopsy.

Intramural calcification apparently represents an incomplete form of perforation and occurs when meconium is extruded into the wall of the intestine through an ulceration. This has been described in rare instances in association with small bowel atresia, volvulus and fibrocystic disease of the pancreas.

Disease Simulating Small Bowel Obstruction

Because it is difficult or impossible in many cases to differentiate between distended small bowel and colon on survey films of the neonatal abdomen, lesions of the large bowel may simulate low small bowel obstruction. The clinical manifestations are also similar and usually provide no reliable means for differential diagnosis. In this instance it is always worthwhile to examine the abdomen in the lateral projection since in this view the long sweep of the descending colon may occasionally be identified in the prevertebral area (19). When the colon cannot be so identified a barium enema examination is imperative to exclude a large bowel obstruction.

Hirschsprung's disease in the neonate presents as intestinal obstruction (20). Although initially well, infants with this disorder usually become distended and vomit bile stained material within the first 36 or 48 hours. The passage of meconium is delayed and the clinical picture is that of intestinal obstruction. Survey films of the distended abdomen may show numerous gas filled loops of intestine with air fluid levels (Fig 24). Differentiation between small bowel and colon is usually difficult or impossible and barium contrast examination of the colon is necessary. In some instances the barium enema films may show a transitional zone in the colon representing a change from the narrower distal aganglionic segment to a dilated ganglionic portion. The aganglionic segment usually extends somewhat proximal to the actual site of transition as demonstrated radiographically. In many instances, however, the colon in the newborn will show a normal calibre throughout with no evidence of a transitional zone. In either case the microcolon seen in distal small bowel atresia (or meconium ileus) is excluded and a normal position of the cecum rules against a malrotation with small bowel volvulus.

When the barium enema shows a colon of uniform calibre delayed films are of the utmost importance since patients with aganglionosis show very poor evacuation on films made 24 and 48 hours after the enema study (Fig 25). In the neonate, radiographic diagnosis of Hirschsprung's disease may be made on the basis of this colonic stasis alone. Hope et al (21) have stressed the diagnostic importance of irregular, bizarre contractions of the aganglionic segment and believe that these indentations, which are irregular in both spacing and extent are the result of dysrhythmia produced by the aganglionosis. It is their experience that these irregular contractions are a more frequent finding in early infancy than a well demarcated transitional zone. This has also been our experience but in those instances where there is neither bizarre contractions nor a transitional zone, persistent colonic stasis may be relied upon as a major diagnostic feature.

Long segment Hirschsprung's disease i.e., aganglionosis involving the entire colon and the terminal ileum presents during the first three months of life as

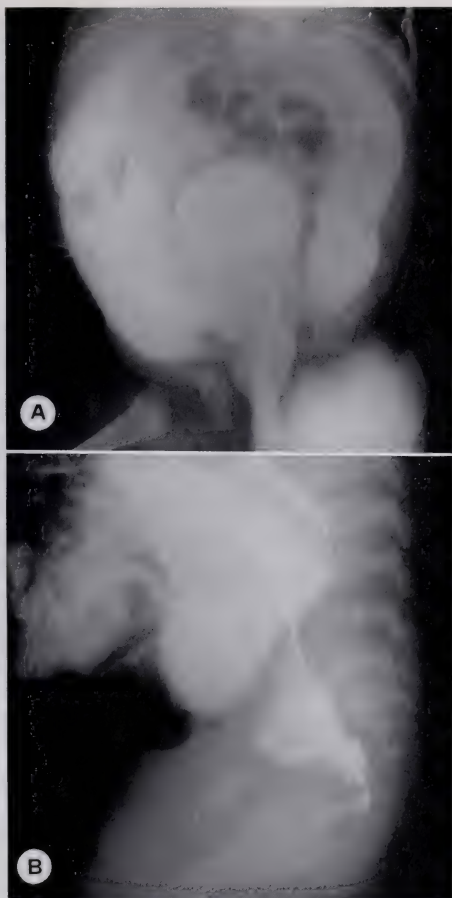


Fig. 25. Hirschsprung's disease diagnosed on 24 hour film. A. Initial barium enema study reveals no obvious transition zone and was interpreted as being normal. B. Twenty-four hours later, lateral film of the abdomen demonstrates marked barium retention as well as a transitional zone within the rectum. Hirschsprung's disease was diagnosed and confirmed.



Fig. 26. Meconium Plug Syndrome. A long filling defect, representing a meconium plug, extends from the hepatic flexure to the rectum. The barium filled colon is of normal calibre. There is, however, a marked degree of small bowel obstruction. The plug was promptly extruded and the patient became and has remained asymptomatic.

an intermittent small bowel obstruction. In these cases the colon is usually of normal calibre, without transitional zones, but shorter than in a normal newborn. Ileal intussusception may be observed on plain films and in barium meal examinations (22).

The meconium plug syndrome may also simulate neonatal small bowel obstruction. In this syndrome, however, there is relief of the obstructive symptoms after digital examination of the rectum or a cleansing enema which dislodges a meconium plug; barium enema examination in these patients often discloses a long plug of obstructing meconium high in the colon and a small

calibre collapsed left colon. Subsequent barium enemas then show a colon of normal calibre and with no bizarre contractions and normal evacuation. When the meconium plug extends to the rectum the colon may be of normal calibre (Fig 26).

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Thio-TEPA and Methotrexate Chemotherapy of Advanced Ovarian Carcinoma

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INTRODUCTION

A chemotherapy-induced regression of ovarian carcinoma may be transiently observed in from 20 to 80% of patients treated with various alkylating agents or antimetabolites (1-13). Single alkylating agent therapy with Thio-TEPA or Chlorambucil has yielded an average response rate of 40 to 50% in several large series of patients in all clinical stages of metastatic dissemination. Nevertheless, many clinicians hesitate to add chemotherapy to the standard armamentarium of extirpative surgery and roentgen therapy because of presumed short duration of tumor suppression and fear of drug toxicity. This is unfortunate since all efforts at earlier recognition of ovarian carcinoma have failed to yield any improvement in the end results of surgery and x-ray treatments during the last two decades (14). Five-year survival rates after surgery (14-16) remain at a low 10 to 30% in most series comprising all clinical stages at laparotomy. The obvious need for more effective palliative measures and a growing awareness of the potential value of chemotherapy has stimulated much interest in the techniques and duration of drug treatment, choice of agents (if any), methods of combining different available drugs, and the relationship of chemotherapy to radiotherapy. This paper will present a six-year experience with the combination of Thio-TEPA and Methotrexate and will briefly review and assess some of the diverse aspects of ovarian cancer chemotherapy.

Ovarian carcinoma represents a uniquely valid testing ground for cytotoxic chemotherapy when the neoplasm is characterized by gross and massive dissemination of upper abdominal metastases with or without ascites (Stage IV v.i.). The consistently feeble effects of surgery and modern super-voltage radiotherapy (14-18) on this cohort of fresh postoperative Stage IV patients provides a reliable retrospective historical control (parameter) by which to assess chemotherapy. The clinician confronted with the symptomatic management of such extensive postoperative or post-biopsy Stage IV neoplasms must attempt to ameliorate the usually progressive course of one to six months of intractable abdominal pain, peritoneal and pleural effusions and terminal episodes of intestinal and renal obstruction. The bulky, easily observable tumor masses with ascites and the relatively short 3 to 4 month median survival of "fresh" postoperative Stage IV cases prior to the era of chemotherapy, offer accurate objective guides to the efficacy of drug inhibition in terms of both tumor regression and host survival. Any favorable effect of chemotherapy alone on these parameters should be readily discernible

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in survival data since less than 10% of Stage IV patients would be expected to live more than one year (14) and less than 5% more than two years without radiation or chemotherapy. In the somewhat selected Stage IV patients who complete a course of supervoltage x-ray therapy (14-18) or are given radiogold, the one-year survival is still less than 30% and the two-year survival is well under 20%—a clear indication of the feeble effects of radiotherapy in disseminated disease.

Staging

Evaluation of chemotherapy for ovarian carcinoma is impossible without consistent and careful designation of the clinical stage and past treatment (19) in each patient, as well as the physical extent of disease.

The following modified staging classification of Walter (20) and Keetal (21) was employed in evaluating designated cases prior to chemotherapy:

Stage I: Neoplasm confined to ovary (or ovaries) in pelvis; completely removed.

Stage II: Neoplasm incompletely removed at surgery or recurrent less than six months after surgery, but grossly confined to pelvis.

Stage IIIA: Late recurrence six months or more after surgery and/or radiation therapy, but still confined to pelvis.

Stage IIIB: Late recurrence disseminated above pelvis or outside abdomen.

Stage IV: Fresh postoperative or post-biopsy with diffuse involvement in upper abdomen with or without ascites, pleural effusions, etc.

We have found it desirable (19) to emphasize the difference between fresh postoperative abdominal metastases (Stage IV) compared to late recurrent pelvic and/or suprapelvic metastases (Stage III). The metastatic disease recurrent in the pelvis (IIIA) or in upper abdomen (IIIB) months or years after surgery and/or radiotherapy was much less predictable in response and survival after chemotherapy than the often massive "fresh" postoperative Stage IV disease although both Stage IIIB and IV may at certain times show an equal physical extent of metastases.

The one-year survival after onset of chemotherapy in late recurrent Stage III varies widely, is unpredictable and may exceed 40% (19) in contrast to the much shorter 3 to 10% survival expected in "fresh" postoperative Stage IV patients receiving no radiotherapy or chemotherapy. Longer-than expected survival of Stage III after chemotherapy may be due not only to the inhibitory effect of the chemotherapy itself, but also could reflect an originally slower growing neoplasm, the fortuitous earlier detection of recurrent disease with smaller or less bulky metastases, or the favorable influence and previous efficacy of radiotherapy in altering the "tumor bed" and pelvic blood supply. These factors could account for a slower advent of intestinal obstruction or other terminal events in Stage III compared to Stage IV. In contrast, any shorter than expected survival of Stage III disease after onset of chemotherapy could represent a manifestation of biological resistance in chronologically older metastatic disease.

When comparing our studies with previous reports it should be noted that many authors (17, 18) designate a single broad clinical Stage III classification to include all advanced cases, i.e., both late recurrent suprapelvic IIIB metastatic disease with the "fresh" postoperative IV cases. Others, notably Munnell and Taylor (14) include our Stage III (recurrent) and Stage IV (fresh) cases in a broad Stage IV designation of suprapelvic disease, but split our Stage I into separate Stages I and II. Some designate a Stage IV to include our Stage IIIB. Since previously untreated massive upper abdominal Stage IV disease is potentially less resistant and less variable than the chronologically older, more resistant but less predictable recurrent Stage III disease, the most consistent data on the effect of chemotherapy can be obtained in the cohort of Stage IV patients treated with chemotherapy alone immediately after initial diagnosis of non-surgically resectable suprapelvic extensive tumor metastases.

Previous Studies

The potential value of systemic alkylating agents for ovarian carcinoma was first demonstrated in 1952 by Rundles and Barton (22) with oral triethylene melamine (TEM) and by Seligman et al (1) with intravenous hemisulfur mustard (2-chlor-2 hydroxydiethylsulfide). Four years later, Sykes et al (2) reported eight cases of objective tumor regression and 14 with temporary symptomatic response among 26 patients treated with oral TEM. Seligman noted that the response to hemisulfur mustard was better after intravenous than after intraperitoneal administration—an observation consistently found with other oncostatic agents as well. Hemisulfur mustard induced transient relief of ascites and short-term symptomatic responses in 9 of 14 of Rutenberg's (3) patients and in 21 of 30 treated by Green (4). Substantial reduction of tumor masses was observed in 8 of Green's cases. Despite these encouraging results showing transient inhibitory responses in as many as 70% of cases, it was not feasible to continue further use of these early alkylating agents because of severe neurotoxicity (HSM) and unpredictable hematopoietic depression (TEM).

Since 1959, the long-acting parenteral alkylating agents Thio-TEPA (thiophosphoramidate) (9) and the oral Chlorambucil (8) (Leukeran) have been reported to inhibit from 30 to 70% of cases of ovarian cancer. Karnofsky and others (23) have concluded that there is probably no single preferred alkylating agent. Cross-resistance between Thio-TEPA and Chlorambucil appears to account for a similar average rate of 40 to 50% responses with either alkylating agent. A 35% response rate after Cytosan was reported by Frick et al (10) to be similar to that after Thio-TEPA. However, more recently the same investigators reported as high as 70% responses after Cytosan (12).

Synergistic additive therapeutic effects exerted by two antineoplastic agents acting by different mechanisms, viz., an alkylating agent and an antimetabolite (antifol) were first demonstrated many years ago by Skipper et al (24) and by us (25) in an experimental leukemia in 1951–1952. In these synergism

studies the net toxicity from two individually toxic drugs given at *adequate* therapeutic dose levels was not additive to the host, although both survival and tumor regression showed marked enhancement compared to results after single drug treatment.

In an early clinical survey of folic acid antagonist chemotherapy in 1952, we found (26) that Methotrexate was ineffective in four cases of mucus cell ovarian carcinoma. The possibility that antifols might exert an antitumor effect in ovarian carcinoma seemed remote until we observed (27) a case of rapid disappearance of pulmonary and abdominal metastatic papillary serous cystadenocarcinoma after treatment with Methotrexate (27) alone. This observation stimulated study (19) of the sustained simultaneous effects of Methotrexate (MTX) with Thio-TEPA (TP) from 1959-1961 in 35 patients with Stage II, III, IV ovarian carcinoma. The double drug regimen consisted of priming and maintenance Thio-TEPA concomitantly with repeated intermittent courses of oral Methotrexate. This antimetabolite-alkylating agent combination induced strikingly rapid and relatively sustained major regressions of massive abdominal tumors among two-thirds of 23 fresh Stage IV cases receiving no radiotherapy, radiogold or extirpative surgery. The overall response rate of 70% appeared slightly better than the usual 40 to 50% level expected from Thio-TEPA, Chlorambucil or Cytosan alone. Because a large proportion of the good and excellent responders remained in remission for more than six months on this combined regimen, the synergism study was extended for four more years to include 103 patients. Three-fourths of these patients were suffering from Stage IV ovarian cancer. The double drug treatment with Thio-TEPA and Methotrexate has been supplemented since 1962 with continuous hematostimulative and anabolic supportive therapy (v.i.). This long-term study was expected to yield more definitive data on: (a) incidence of initial regression after simultaneous alkylating agent-antimetabolite treatment, (b) duration of sustained clinical remission on combined maintenance chemotherapy, (c) value of hematostimulative and anabolic measures in enhancing tolerance to drug combinations, and (d) response, if any, to subsequent agents in combination particularly the phosphamidase-activated alkylating agent Cyclophosphamide, and the antimetabolite 5-FU after appearance of resistance to the Methotrexate-Thio-TEPA combination.

Procedure

Priming and maintenance Thio-TEPA and intermittent Methotrexate therapy was instituted in 103 patients with ovarian carcinoma. There were 70 Stage IV, 26 Stage III and 7 Stage II cases in this study. Ninety-six patients received two or more courses of MTX. Combination TP + MTX therapy was maintained for as long as 4½ years. Eighty-two patients began treatment more than three years before presenting this paper. Eighty-five of these patients were hospitalized at The Mount Sinai Hospital on private or ward services. Seventy-two cases (Group II) since 1961 were given continuous hematostimulative therapy (v.i.). Combination TP + MTX therapy was usually

begun four to seven days postoperatively in Stage IV cases, but occasionally as early as two days after laparotomy. The priming or loading dose of Thio-TEPA consisted of 60 mg given intramuscularly in 15 mg doses daily or occasionally spaced 48 hours apart. The individual oral daily divided dose of Methotrexate was based on a total aggregate dosage per week ranging from 0.25 to 1.5 mg per kg (15 to 125 mg total dose). The lower aggregate dosages were employed for the worst "poor-risk" patients, i.e., those with poor renal function, fever, cachexia, diarrhea, azotemia, evidence of massive or recent radiation therapy, severe anemia, prior drug treatment, severe anorexia or mental depression or age above 65 years. Patients with a previous history of major gastrointestinal bleeding were not accepted for combined treatment with the folic acid antagonists (MTX). The daily MTX dose ranging from 5 mg to 12.5 mg was always administered orally in divided 2.5 mg doses until the first signs of stomatitis appeared. These initial toxic signs usually consisted of burning mouth or the development of flat, white atrophic areas of epithelium on the buccal mucosa, tongue or lips. Methotrexate was never administered each day until the patient had been carefully examined for any signs of impending antifol toxicity. The first signs of an oncoming stomatitis were considered as the main reliable early indication that dosage would be sufficient to produce the desired folic acid deficiency state. Stomatitis often preceded leukopenia by several days or more as noted previously in other solid tumor patients (28). The aim was to gradually induce the toxic deficiency state ("antifol titration") yet to avoid severe depressive hematopoietic effects by abruptly stopping the drug at the first sign of any upper gastrointestinal tract effect. The toxic deficiency state usually became more intense on the second or third day after prompt withdrawal of further Methotrexate. Transitory anorexia usually developed as part of the "antifol state" which in many instances was accompanied by nausea and crampy abdominal pain. Vomiting, severe ulcerative stomatitis, esophagitis, low grade fever and rash appeared in decreasing frequency (19) as manifestations of a more than optimum toxic state. Although recovery was often clinically complete within five to seven days after withdrawal of Methotrexate, the second course of MTX was usually withheld until the third or fourth week after the initial Thio-TEPA-Methotrexate combination had been commenced. The aggregate dosage of the second course of Methotrexate was 20 to 25% larger than used in the first course of Methotrexate if an improved clinical and nutritional state had been induced by the initial TP + MTX therapy. Tolerance to Methotrexate after tumor regression was often improved apparently due to larger endogenous reserves of folic acid metabolites. Maintenance Thio-TEPA was begun in the third week after the initial treatment at a dose of 15 mg i.m. once per week. Small increases in this weekly Thio-TEPA dosage were given if no leukopenia had been produced by the end of the first month of chemotherapy. After the first month, dosage was titrated to maintain a chronic leukopenic state with leukocyte counts between 3000 and 4000 per cu mm. It was usually possible to widen the interval between each 15 mg Thio-TEPA injec-

tion to from 10 to 21 days after the third month of combination chemotherapy. Conclusions regarding the efficacy of the chemotherapy combinations were held in abeyance until the patient had received a minimum of two courses of Methotrexate together with the necessary amount of Thio-TEPA to maintain a modest leukopenia in the second month of chemotherapy. A third course of MTX was given in the fourth month of chemotherapy. The fourth and fifth courses of MTX were given between the sixth and tenth months of chemotherapy if remission continued. Continuous hematostimulative therapy consisting of 50 to 100 mg of aqueous crystalline testosterone plus 100 μ g of B12 intramuscularly each week with minimal oral doses of prednisone (5 to 10 mg per day) was employed in all patients treated between 1962-1965. Cytosan therapy alone or in combination with 5-Fluorouracil was administered to all cases as previously outlined (19) when resistance to the TP + MTX combination had developed.

RESULTS

Results of TP + MTX combination chemotherapy (Table 1) were classified as follows:

Excellent: Essentially complete gross disappearance of all signs (i.e., 80-99% regression) of tumors, ascites, pleural effusions, etc., for at least six months.

Good: Substantial (50-80%) decrease in size of tumor masses for six months or longer but without gross clinical disappearance of neoplasm.

Fair: 20-50% reduction of tumor masses with much improved performance status for three to twelve months.

Equivocal: Transient partial regression of less than three months duration.

None: No effect on tumors or progressive course.

Toxic Death: Death in four weeks after onset of therapy with signs of profound bone-marrow depression.

From 1959-1965 ninety-six of a total of 103 patients completed a minimal course of combination chemotherapy (Table 1) consisting of the priming and maintenance doses of Thio-TEPA, plus at least two courses of Methotrexate, three to six weeks apart. Three induced toxic deaths occurred in poor-risk patients within 2-4 weeks after the initial course of TP + MTX therapy. No deaths have been induced in the last 69 consecutive cases treated. Two patients refused to complete a second course of MTX due to a psychologic depressive reaction precipitated by alopecia. Forty-three excellent and 17 good objective regressions were obtained among 96 adequately treated patients. Six fair regressions were also induced. Results were equivocal in 4 and negative in 26. Sixty-six of 96 or 73% of all adequately treated cases showed significant objective tumor regression. Responses of longer than six months, i.e., symptom-free excellent or good sustained major regressions were obtained by the combination chemotherapy in 60 of these 96 patients. The response rate of 44/64 obtained in the second series treated since 1962 was not better than the

21 of 32 responses induced in the earlier series from 1959-1961. Thus, the two-thirds rate of objective response was verified but not improved in the more recent series. The rapid tumor-regressing effect of the TP + MTX combination split the cases promptly into responders or non-responders. The 43 excellent regressions exceeded the 17 good responses and contrasted with only a small group of 6 partial regression. Thirty were failures or showed equivocal response. The major sustained objective regressions ("excellent or good") were obtained in 57 of 68 cases of papillary and serous cystadenocarcinoma (Table 2), compared to only three such responses among 37 miscellaneous types of ovarian neoplasms. The single case of granulosa cell tumor in our series showed a striking regression of massive tumors which was sustained for eight months. Only one patient among nine with adenocarcinoma responded with a 14-month regression. One 18 year old girl, among three cases of teratocarcinoma showed an excellent regression for six months before recurrence. The fair and equivocal responses and the failures were observed in cases of pseudomucinous, anaplastic, teratocarcinoma, Brenner Cell, mucus cell, adenocarcinoma (Krukenberg) and adenocarcinoma.

Regressions became obvious clinically among all the responders within 10 to 20 days after onset of TP + MTX chemotherapy. There was no relation of age or duration of untreated disease to the response obtained after combination chemotherapy. This was illustrated by excellent tumor regressions induced in four patients who had presented with very slow-growing papillary neoplasms characterized clinically by more than six months of abdominal swelling prior to laparotomy and microscopically by diffuse psammoma bodies.

The average duration of regression among the 66 responders was 11.5+ months (median 10.5+ months) and survival 17.4+ months (Fig 1). The non-responders including fair and equivocal responses, lived an average of 6.2 months after exploration (median 5.1 months). A one-year longer survival was thus obtained in the responders compared to the non-responders (Fig 1).

Improved quality of survival with little or no morbidity or symptoms, i.e., 'guarantee time', was the conspicuous clinical feature of the responders in the recent series maintained on treatment since 1961 (Fig 2). The one-year survival in the first series of 23 Stage IV cases treated 1959-1961 was only 35% (Table 3).

In this earlier group only one patient lived for more than two years after diagnosis. This compared with more than 60% survival at one year (Table 3) and more than 30% survival after two years at the time of this report (Dec., 1966) among 47 Stage IV cases treated from January, 1962 to June, 1965. The proportion of papillary and serous carcinomas was the same in both groups as was the extent of disease at the time of diagnosis (Table 4). The major obvious difference between the two series was the routine use of the hematostimulative and hormone support in the more recent group. Better hematologic tolerance to the repeated cycles of MTX while on continuous Thio-TEPA therapy was observed since 1962 especially in the maintenance of

TP+MTX THERAPY OVARIAN CARCINOMA

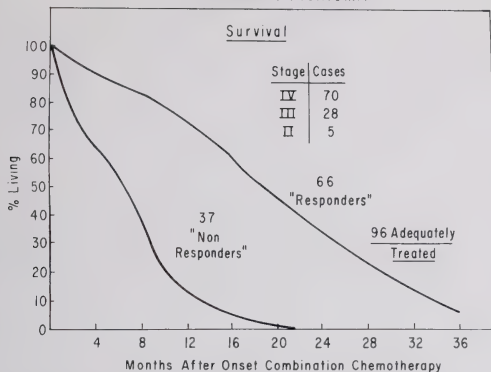


FIG. 1. Survival curve of 66 excellent, good or fair responders compared to survival of 37 equivocal or non-responders.

TP+MTX THERAPY OVARIAN CARCINOMA

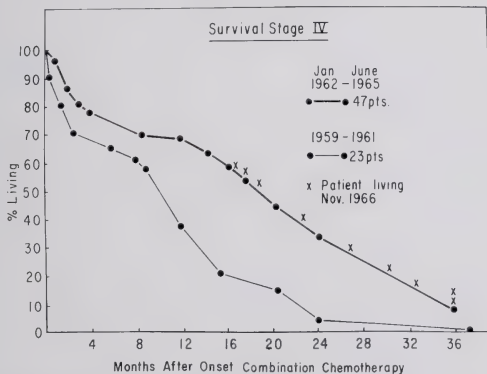


FIG. 2. Improved survival of 47 Stage IV patients treated since 1962 compared to survival of 23 Stage IV patients prior to 1962.

satisfactory erythrocyte and platelet levels. Three drug-induced deaths occurred in the first 34 patients but none in the last 69 cases. During the first six months of chemotherapy the number of MTX courses given was similar in both series. However, more patients since 1962 received a total of 4 to 6 courses of MTX before recurrence developed in the period from six months to one and one-half years after onset of chemotherapy. A substantially larger total dosage of both Methotrexate and Thio-TEPA was administered to the recent patients compared to the early group, and the dose of MTX during the first course was more rigidly controlled in poor-risk patients.

DISCUSSION

The rapid response of papillary and serous cystadenocarcinomas to the combination of TP + MTX originally observed in our preliminary study (19), was confirmed in this large experience over a six-year period. The anti-tumor action of TP + MTX became evident in Stage IV papillary and serous cystadenocarcinomas by the marked reduction of large tumor masses and disappearance of ascites when the "antifol" effect became obvious a few days after stopping the daily oral MTX in the first course. An inhibiting effect of folic acid antagonists alone on advanced ovarian cancer has not been heretofore generally recognized. A current "reevaluation" of Methotrexate (29) by Sullivan and Oberfield mentions that five of sixteen cases of ovarian carcinoma showed some response to MTX alone. The individual effects of the alkylating agent could not be clearly distinguished from the effect of the antimetabolite (MTX) during the simultaneous use of both drugs in our studies. Two large series of Stage IV cases treated at length with MTX or TP would have been necessary to reliably assess the potency of each individual agent alone. The number of clinically significant responders was not markedly increased by the addition of the antimetabolite (MTX) to the alkylating agent (TP) since at least 50% would have been expected to show a transient response to the Thio-TEPA (or Chlorambucil) alone. An additional 20% of patients could represent tumors brought under objective control by use of the TP + MTX combination. However, it should be noted that Lebharz (32) was able to produce sustained palliation in 69% of 26 cases by employing Chlorambucil therapy at levels sufficient to maintain substantial leukopenia. The regression rate of 73% after TP + MTX appeared limited by the number of papillary and serous adenocarcinoma available for treatment. The addition of Cytoxan and FU after failure of two or more months of TP + MTX therapy did not produce a single additional good or excellent regression (six months or longer). The second set of cytotoxic drugs did not widen the spectrum of antitumor effectiveness at least in the combination interval and sequence employed. Thus, the number of mucus and adenocarcinomas, teratomas, etc., rather than the number of drugs employed limited the overall rate of major sustained clinical regression. Investigators using alkylating agents alone have not mentioned a dependence of response on

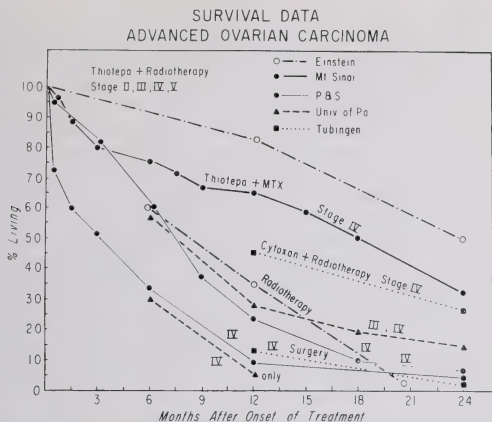


FIG. 3. Comparative Survival Data in advanced ovarian carcinoma treated at five different institutions by surgery, radiotherapy and/or chemotherapy. The 5-15% one-year survival after surgery alone was exceeded by the 25-35% survival among cases receiving radiotherapy. Several different series show much improved survival after chemotherapy with or without radiotherapy (see text for detailed discussion).

papillary and serous histologic types. The relative resistance of teratomatous tumors has been noted by Masterson (8).

The improvement in survival achieved by sustained Thio-TEPA and Methotrexate therapy for the average patient with widespread ovarian cancer compares favorably with radiotherapy end-results. Stage IV patients who formerly had a 5 to 10% chance after surgery (Fig 3) and not more than a 15 to 35% survival after supervoltage radiotherapy appear now to have at least a 60% chance to survive one year with combination chemotherapy (Fig 2). Among the 60% who respond and survive one year, about half or 30% will live two or more years. Patients with papillary and serous adenocarcinomas can expect a year longer survival (Fig 1) than non-responders after combination TP + MTX therapy.

The pathologic distribution, stage and extent of metastases and method of administering TP + MTX were similar in the 1962-1965 group (Fig 2) as in the earlier 1959-1961 group (Fig 1). The absence of lethal drug toxicity in the last three years seemed to reflect an improved skill and greater caution in judging drug dosage during the initial course of combined drugs. A more critical analysis of the medical risk factors, especially renal function, age and nutritional status in each individual case prior to setting the dosage for the initial oral course of MTX probably accounts for the lack of recent drug deaths.

The antimetabolite plus Thio-TEPA action always produced a chronic leukopenic state maintained after the second course of Methotrexate. Testosterone, B12 and small oral doses of adrenal steroids appeared to delay the development of clinically significant anemia or thrombopenia despite the fact that all cases (Group II) were maintained in a chronic leukopenic state. The responders who were given the supportive hematostimulative and anabolic therapy postoperatively usually achieved normal hemoglobin levels with minimal masculinization despite continuing leukopenia-inducing chemotherapy. This favorable hematologic tolerance had permitted the responders since 1962 to receive more courses of MTX during the second six months of chemotherapeutic management. The improved survival of the recent patients compared to the similar group from 1959-1961 (Fig 2) is assumed to be due to the more intense and sustained chemotherapy recently employed.

At casual glance the net effect of antimetabolite-alkylating agent therapy on initial response rates (70%) did not appear definitely better than the best response rates reported after single alkylating agent therapy. However, the antitumor synergism offered by TP and MTX seemed evident by the rapid speed of induction of major regressions of diffuse massive Stage IV metastases. In addition, the relatively long asymptomatic control ('guarantee time') provided by the combined maintenance therapy in the cohort of postoperative Stage IV patients seems also to reflect an antitumor synergism. The more effective action of TP + MTX is suggested by comparison of the duration of survival and the extent of regression of various large series of predominantly Stage IV cases. At the New York Presbyterian Hospital, Frick (12) obtained only 35% of objective responses to Thio-TEPA for one month or longer and only 15% for more than six months. Only one patient among 104 cases remained in remission for more than one year. Less than 3% lived beyond two years. Nevertheless, this chemotherapy consisting for the most part of single courses of Thio-TEPA, yielded a 5-month improvement in mean survival (12) compared to similar cases selected for radiotherapy alone prior to the use of Thio-TEPA. Similar low one-year survival rates were also reported by Keetal (30) after Chlorambucil therapy. A more prolonged regimen of oral alkylating agent therapy (Chlorambucil) produced 50% objective remissions of at least six months duration in Masterson's series. Yet, only 14% of Masterson's patients (8) remained in remission after two years despite an almost equal distribution of Stage II, III, IV cases. The longer persistence of control by combination therapy is also indicated by comparison with data (31) at the University of Oregon. Only 3 of Ray's 37 Stage IV cases were alive and free of disease one year after sustained intensive Chlorambucil or Thio-TEPA therapy. Vigorous Chlorambucil therapy in a series with a substantial number of Stage II cases, yielded 69% responses for 9 months or longer (32) with a median survival of 20 months provided that the white blood count was maintained in the 2500-4000 range.

Strict comparison of these single drug studies with TP + MTX is not feasible unless a similar proportion of Stage IV cases are included at onset of treat-

ment in each series. No other treatment center has yet reported on combination TP + MTX therapy in the management of advanced ovarian carcinoma. Additional studies are desirable to confirm the extent of prompt control achieved by combining the antimetabolite (MTX) with a single alkylating agent (TP). Totally unanswered is the question whether better palliation can be maintained by alternation or serial use of these two agents in asymptomatic patients under apparent clinical control.

Relation of Chemotherapy to Radiotherapy

Retrospective data and simultaneous studies from diverse sources now indicate that the sustained palliation and survival provided by chemotherapy is definitely better than deep x-ray therapy alone in postoperative patients with diffuse abdominal metastases (Stage IV). Not a single one-year survivor was obtained at the Ochsner Clinic among 41 inoperable or incompletely removed tumors treated with supervoltage radiotherapy and/or radiogold (15). A low one-year survival of 15 to 35% was found in Stage IV patients receiving therapy at the Presbyterian (N. Y.) Hospital, the University of Pennsylvania and the University of Tubingen (Fig. 3). Maintenance Chlorambucil therapy added to radiotherapy improved survival by at least five months compared to survival after radiotherapy alone (12). Sustained Cytosan therapy (Endoxan) combined with radiotherapy (18) resulted in an eight-month average increase in survival (Fig 3) for Stage IV patients. However, the survival after chemotherapy + radiotherapy was not better than we obtained in Stage IV by the combined use of Thio-TEPA and Methotrexate without postoperative radiation (Fig 3). The sustained diffuse systemic effect of chemotherapy probably accounts for this more effective control of disseminated metastases.

Definitive studies are not yet available on the optimum time relationship of radiotherapy to chemotherapy. No significant differences in results were observed (32) when radiotherapy preceded or followed a course of priming Chlorambucil therapy. Schwartz et al (33) employed Thio-TEPA simultaneously or subsequent to radiotherapy in a large series with recurrent disease in all clinical Stages (II, III, IV). Their mixed group showed satisfactory hematologic tolerance and excellent survivals, i.e., 80% at one year and 50% at two years (Fig 3). No undue toxicity was observed after the combination of Cytosan plus radiotherapy in Stage IV patients. Pelvic radiotherapy through limited abdominal portals for residual or recurrent pelvic metastases, after single alkylating agent therapy, has evidently been tolerated at effective drug levels without undue hematologic toxicity. However, the simultaneous use of total "abdominal bath" radiotherapy may result in poor tolerance to chemotherapy (27) despite the adequate use of hematostimulants. The tolerance of recently radiated patients to chemotherapy has been sufficiently limited to require definite reduction (27) in drug dosage, especially in the aged.

Our policy, since the conclusion of this combination (TP + MTX) chemotherapy study, has been to continue to withhold radiotherapy for at least two

months during the immediate postoperative period in Stage IV patients under treatment with intensive combination chemotherapy. Gross eradication of diffuse metastatic disease has made use of diffuse abdominal radiotherapy seem superfluous at this time in treatment of the excellent chemotherapy responders. If the inhibitory effects of TP + MTX on the papillary and serous metastases are clinically incomplete, radiotherapy may be directed then or at a later date through limited portals to any residual tumor masses, usually in pelvis. Radiotherapy for diffuse metastases unresponsive or resistant to the TP + MTX regimen has been consistently disappointing. The subsequent use of Cytosan and 5-Fluorouracil has been likewise ineffective as indicated by the poor two to four month survival of TP + MTX non-responders and in recurrent resistant cases. The clinical circumstances in which an effective relationship of radiotherapy to chemotherapy has occurred has been in those Stage IV chemotherapy responders who developed late local (usually pelvic) recurrence one or two years after showing an initial major regression response to the TP + MTX chemotherapy. These responsive cases with long-term survival probably represent an iatrogenically selected group of chemotherapy-sensitive tumors which are locally controllable with radiotherapy.

Chemotherapy has thus been recently established as the primary therapeutic modality for the clinical management of disseminated ovarian metastases. Although comparison of retrospective noncontrolled studies from diverse institutions is subject to quantitative limitation, the currently available evidence suggests that chemotherapy for Stage IV cases should be employed either before or simultaneously with radiotherapy rather than after radiotherapy. Extensive long-term studies are necessary to determine whether, in patients with pelvic metastases only (Stage II), chemotherapy should be held in abeyance until overt signs of recurrence appear after radiotherapy. Predictable increases in survival in disseminated ovarian cancer are primarily the result of the temporary control of the 70% of chemotherapy-sensitive tumors.

SUMMARY

Combination alkylating agent-antimetabolite chemotherapy consisting of priming and maintenance Thio-TEPA (TP) and intermittent courses of Methotrexate (MTX) was employed in 103 cases of advanced ovarian carcinoma from 1959-1965. Rapid substantial objective regressions of at least six months duration were induced in two-thirds of all patients; conspicuously among most of the postoperative disseminated Stage IV papillary and serous cystadenocarcinomas comprising more than 70% of the cases available in this series. Strict "clinical risk" criteria for Methotrexate dosage together with continuous hematostimulative therapy (androgens, B12 and small doses of oral steroids) provided improved hematologic tolerance thus permitting more sustained chemotherapy with minimal drug toxicity since 1962. The one-year survival improved from 35% between 1959-1961 to 60% from 1962-1965, with a similar proportion of Stage IV patients in both series. The one and

two year survival after maintained combination TP + MTX chemotherapy far exceeds the results of radiotherapy alone.

The rapidity and extent of regression and the survival in Stage IV patients treated with TP + MTX appeared better than reported by others after Thio-TEPA or Chlorambucil alone, although the initial response rate after intensive single alkylating agent therapy may approach the 70% response rate obtained with combination (TP + MTX) chemotherapy.

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TABLE 1
Results

<i>Total Treated</i>	103
Toxic deaths.....	3
Refused to continue.....	2
Lost.....	2
Adequately treated.....	96
<i>Regression</i>	
Excellent.....	43
Good.....	17
Fair.....	6
Equivocal.....	4
None.....	26
<i>Survival</i>	
1 year.....	63/96
2 years.....	24/81*

* 13 Living, December, 1966, more than 17 months after onset of chemotherapy.

TABLE 2

Pathological Diagnosis	No. of Cases	Excellent or Good Responses
Papillary serous cystadenocarcinoma.....	68	57
Pseudomucinous adenocarcinoma.....	3	0
Adenocarcinoma.....	9	1
Anaplastic carcinoma.....	6	0
Brenner cell.....	1	0
Teratocarcinoma.....	3	1
Granulosa cell.....	1	1
Mucus cell adenocarcinoma (Krukenberg).....	5	0
Total.....	96	60

TABLE 3

	Survival (1 Year)	Stage IV (2 Years)
1959-1961		
23 Cases.....	35%	4%
1962-1965		
47 Cases.....	66%	29+%

TABLE 4

Distribution of Clinical Stages

	1959-1961	1962-1965
Stage II.....	3	4
Stage III.....	9	17
Stage IV.....	23	47
Total.....	35	68
Adequately treated.....	32	64

Therapy With Radioisotopes: A General Survey (Excluding Iodine) *

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The discovery of artificially induced radioactivity in 1934 marked the opening of a new era for the therapeutic exploration and exploitation of radioactive phenomena. In 1938 John Lawrence introduced the first successful use of an artificially produced radioactive material, radioactive phosphorus (^{32}P), for the treatment of leukemia and, subsequently, polycythemia vera (1, 2). Thirty years have thus elapsed since the first therapeutic use of cyclotron produced radioactive isotopes.

To be of value therapeutically, an internally administered radioisotope must be selectively accumulated and homogeneously distributed in the tissue(s) to be irradiated, as compared to normal tissues, and should have a suitably short biologic half-life and suitable radiation spectrum. In employing radioactive substances, as in other forms of radiation therapy, one must be as conscious of sparing normal tissue as one is of destroying malignant or other target tissue. With the exception of radioiodine, which will not be considered here, and, to a limited degree, radiophosphorus, therapeutically useful selective uptake and retention have not been readily accomplished by the administration of radioisotopes. Many ingenious and resourceful attempts have been and are being made in the search for radioactive agents capable of seeking out neoplastic tissue and inhibiting its growth. Thus far, success has been limited. Nevertheless, isotopes of a variety of elements, in a variety of forms, and administered in a number of different ways have played and continue to play an important role in the therapy of both malignant and non-malignant disease, as the treatment of choice or as a valuable alternative or useful adjunct.

In 1955 John Lawrence presented a twenty year survey of the use of radioisotopes in the therapy of cancer (3). The figure is adapted from his paper and has been brought up to date. Almost as many isotopes are no longer used in therapy as have been added to our armamentarium. Nevertheless, important new uses have been found for old isotopes and many advances have been made, particularly in the areas of teletherapy and brachytherapy. Cesium 137 teletherapy sources are playing an increasingly important role in external beam therapy for treatment at short source to skin distances, especially about

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and efficient as a means of delivering supervoltage energy radiation to deep-seated tumors (6, 7).

The very desirable 33 year half-life of the fission product cesium 137 and its relatively soft gamma emission are among the important physical and technical considerations that have led to its increasing use. Cesium 137 teletherapy sources cannot be produced with the same high source strength and specific activity as cobalt 60, but cesium units have been found to be very satisfactory for the treatment of superficial lesions at short source to skin distances where flexibility is desirable (4).

A disadvantage in the use of these radioisotope sources for teletherapy is their constant decay, necessitating dose rate corrections and periodic source replacement. This is much more of a problem for the 5.3 year half-life of cobalt 60 than it is for the longer-lived cesium 137. Since decay is exponential, however, the exposure dose rate can be precisely calculated and predicted. The precise knowledge of the output from an isotope source is an advantage over the fluctuations known to occur with the supervoltage x-ray generators and particle accelerators. In addition, isotope units are not subject to the mechanical problems and constant technical care and upkeep required by electrical generators.

INTERSTITIAL AND INTRACAVITARY USE OF SEALED GAMMA AND BETA-EMITTING SOURCES

Several notable advances have been made in the use of artificial radioactive isotopes in interstitial implantation, intracavitary, and contact therapy employing sealed gamma or beta ray sources. Radium applicators remain the prototype system for many interstitial and intracavitary applications, such as in the treatment of carcinoma of the uterine cervix. Radium sources are permanent, they never need calibration, they are always available, and they are economical for busy treatment centers. Implantation patterns and dosimetry are firmly established and proved. Radium, however, has many recognized disadvantages.

The last decade has seen significant advances in improving and increasing the applicability and decreasing the hazards of brachytherapy. These advances have been primarily of two forms. First, a number of radium substitutes have been developed and techniques devised for exploiting the versatility and flexibility they possess, as compared with radium and its radioactive daughter isotopes (5). The radium substitutes and some of their characteristics are outlined in the Table. Second, radiation hazards have been substantially reduced and personnel protection simplified by virtue of the favorable radiation properties and fewer contamination problems of some of these newer isotopes (e.g., iridium 192 and cesium 137), and by the development of techniques for "after-loading" of the active radiation sources into pre-placed applicators (8, 9).

One of the principal disadvantages of radium is the considerable radiation hazard associated with its handling and use, and the inconvenient pro-

protective measures required to shield the radiation therapist and other personnel from its penetrating gamma rays. In addition, the rigidity and fragility of radium needles makes them completely inflexible. Ideal implantation patterns and dose distribution may therefore be difficult if not impossible in large irregularly shaped or relatively inaccessible tumors. The dangers of leakage and breakage, with the resulting serious radiation hazard and problem of contamination also constitute drawbacks when compared with the radium substitutes.

Cobalt 60 and tantalum 182 offer no advantage over radium in terms of the radiation hazard and protection problems associated with their use. This can be seen by comparing their gamma ray energies and half-value layers (Table 1). The high specific activity of cobalt 60 sources, however, has been used to advantage in the preparation of thin cobalt wire sources for after-loading into pre-placed rigid applicators or flexible nylon ribbons for interstitial therapy (10) and in the preparation of compact, high activity sources for after-loading in intracavitary therapy (9). Flexible tantalum 182 wires have been found useful for removable interstitial implantation of bladder neoplasms and accessible irregularly shaped tumors (11, 12).

Iridium 192 (^{192}Ir) in the form of wire seeds that can be after-loaded into thin nylon tubing with the thickness of heavy chromic catgut appears to be the most promising radium substitute for flexible interstitial implants (5, 13, 14). Protection from the soft gamma radiation of ^{192}Ir (average gamma energy about 400 kev) is much easier than for the much more penetrating gamma spectrum of radium. The great accuracy made possible by the use of flexible, after-loaded iridium 192 sources, plus the significantly lessened radiation hazard associated with their use has expanded the applications of interstitial gamma ray therapy and constitutes a real advance in this field.

Sources of cesium 137 are also desirable substitutes for radium for use in intracavitary applicators and in removable interstitial implants where rigid needles are suitable (15, 16). Its gamma energy is only about half that of radium, thus simplifying protection problems; its half-life is very favorable for long-term use without continuous corrections for decay; and its use is not as-

TABLE 1

Radium Substitutes and some of their Characteristics; Isotopes Arranged in Decreasing Order According to their Half-Life

	T 1/2	Gamma Ray Energy (mev)	Half-value Layer (lead) (cm)	K Factor (r/hr/mc at 1 cm)	Production
Radium 226.....	1600 y	0.05-2.4	1.2	8.2	—
Cesium 137.....	33 y	0.66	0.5	3.3	fission
Cobalt 60.....	5.3 y	1.17, 1.33	1.2	13.4	n capture
Tantalum 182.....	115 d	1.12-1.22	1.0	6.1	n capture
Iridium 192.....	74 d	0.3-0.6	0.3	5.5	n capture
Radon 222.....	3.8 d	0.2-2.2	1.2	8.2	—
Gold 198.....	2.7 d	0.411	0.3	2.4	n capture

sociated with the dangers of leakage or breakage as in the case of radium needles.

In 1964 the National Advisory Committee on Radiation (17) endorsed the use of cesium 137 sources as a substitute for radium needles in interstitial implantation therapy. Because of the vast amount of clinical experience that has been gained with radium it was recommended that such sources should conform, insofar as possible, to the dimensions and dose distribution patterns of existing radium sources. For temporary interstitial therapy, where flexibility and shielding are important considerations, iridium 192 was considered to be the most suitable choice for most applications.

Gold 198 seeds have almost completely replaced the older radon seeds for permanent interstitial implantation therapy (18). Radioactive gold seeds may be prepared in the desired size and strength depending on the requirements at the time of implantation. The half-value layer in lead for the 0.4 mev gamma rays of gold 198 is about one quarter that for the more energetic gamma spectrum of radon. In addition, the problems created by the gaseous nature of radon are obviated by the use of metallic gold. Thus, the production, handling and use of gold seeds presents much less radiation hazard than for the older radon seeds. A clever implantation "gun" has been devised for increasing the speed, ease and safety of gold grain implantation (19, 20).

The introduction of isotopes that decay by electron capture has been another valuable contribution to the problem of radiation protection in implantation therapy. Harper and associates were the first to explore this modality in brachytherapy (21). They studied the use of applicators loaded with a solution of cesium 131 and the direct interstitial injection of palladium 103 in the form of precipitated palladium black. Henschke and co-workers (22) have reported recently on the use of encapsulated sources of cesium 131, iodine 125, and xenon 133. The very low energies of the characteristic x-rays emitted by these electron capture radioisotopes (about 30 kev), with half-value layers in lead of approximately 1/1000 inch, greatly facilitate radiation protection procedures and practically eliminate significant radiation hazard to personnel, while also greatly reducing the integral body dose to the patient.

The parent-daughter pair of strontium 90 and yttrium 90 have found increasing use as a source of energetic beta radiation. Pure beta-emitting strontium 90 applicators have been used frequently for surface contact therapy, and have been replacing the older radium moulds for beta radiation of superficial lesions (23). Strontium 90 applicators have enjoyed particularly wide use in ophthalmology as an adjunct to surgery in the treatment of pterygia and in keratoplasty to prevent postoperative corneal vascularization (24).

Radiation hypophysectomy by implantation of the pituitary with pellets, seeds or spheres of yttrium 90 alone or in combination with surgery has been performed in many centers (25-28). The radioactive ^{90}Y sources are accurately localized in the sella turcica by stereotactic techniques or by careful placement monitored by image-intensification fluoroscopy. Implantation has been accomplished by the transcranial, transnasal-transsphenoidal, and para-

nasal-transsphenoidal routes. Radiation hypophysectomy using sources of radioactive ^{90}Y or ^{198}Au has been applied successfully in the treatment of hormone dependent carcinoma of the breast and prostate (26-30), Cushing's syndrome secondary to bilateral adrenal-cortical hyperfunction (31), diabetic retinopathy (32), and malignant exophthalmos (33). The local and metabolic effects of functioning pituitary tumors have also been effectively controlled with radioactive implants (34, 35).

Harper and his associates at the Argonne Cancer Research Hospital have recently reported the development of a nuclear needle, incorporating an active strontium 90 source into the terminal end of a stainless steel needle (36). Strontium 90 (28 year half-life) decays to yttrium 90 by emission of a beta particle of moderate energy. The ^{90}Y decays, in turn, to zirconium 90 with a half-life of 2.67 days by emission of an energetic beta particle (maximum energy about 2.27 mev). This nuclear needle thus serves as a continuous source of high-energy beta particles on a virtually permanent basis. It has been used successfully as a radiation source for implantation hypophysectomy (37) and for the interruption of spinal pain tracts by percutaneous anterolateral cordotomy (38) in patients with intractable pain. The advantages of a nonoperative technique for cordotomy are obvious. By obviating the potential mortality and morbidity of an operative neurosurgical procedure, cordotomy may be offered to a larger number of patients suffering from severe pain associated with metastatic malignancy.

INTERNAL APPLICATIONS

Advances in the application of internally administered radioisotopes in therapy generally have been the most disappointing. In contrast to the remarkable advances made in the diagnostic use of internally administered isotopes and in other areas of radioisotope therapy (39), therapeutically useful selective localization has thus far failed to realize its potentials.

The same isotopes that were in use for internal administration ten years ago are still being utilized in much the same fashion and form (Fig 1). Iodine 131 remains a powerful weapon in the treatment of thyroid disorders and radioactive phosphorus (^{32}P) is an excellent agent for treating polycythemia vera (40-42) and the chronic leukemias (43-45). Radiophosphorus, when administered orally or intravenously as sodium phosphate P 32, is somewhat selectively concentrated by rapidly metabolizing tissues, such as tumor cells, leukemic tissue, and normal bone marrow (46, 47). This selectivity is dependent upon the total exchangeable phosphorus in the tissue, the turnover of phosphorus by the tissue, and the rate of new tissue formation. In about 75% of cases of erythremia treated with radioactive phosphorus the modest selective uptake of ^{32}P in the hyperplastic bone marrow and its eventual deposition in the large calcium phosphate pool of bone result in significant bone marrow suppression and normalization of the hematologic picture within two to three months. Radioactive phosphorus ^{32}P has also been used successfully for the treatment and control of a related myeloproliferative disorder, primary (es-

essential) thrombocythemia (48, 49). Judicious administration of ^{32}P will maintain the platelet count within normal limits and, in so doing, help to prevent the hemorrhagic and thrombotic complications of this disorder.

Of all the agents used for the treatment of polycythemia vera, chronic leukemia, and essential thrombocythemia ^{32}P is by far the simplest to use, from the viewpoint of both the physician and the patient. Results are predictable in the vast majority of cases, there are no unpleasant or undesirable side reactions, remissions are fairly prompt and generally of long duration, as much as 4 to 5 years in some cases, and the patient need be seen at infrequent intervals for follow-up examinations.

In the last few years there has been increasing concern about the possible leukemogenic role of ^{32}P in polycythemia vera (50-53). That an increased incidence of acute leukemia does occur in polycythemia vera treated by ionizing radiation is unquestioned in our minds. In our large series of cases, approximately 11% have died with a syndrome indistinguishable from acute myeloblastic leukemia. In those cases treated without radiation, but with phlebotomies and or chemotherapy, including chlorambucil, busulfan, or cyclophosphamide, not one case of acute leukemia has been observed as yet. However, it must be emphasized that these results are not comparable since the radiation treated group has had a mean survival of about 13 years following diagnosis, whereas the chemotherapy treated group has so far been followed for an average of only about 3½ years.

The diagnosis of polycythemia vera is at times difficult, even today, to establish with certainty, and the leukemic state certainly can be most confusing. A carefully controlled, randomized prospective cooperative study is needed to resolve the many facets of this problem. Ten years from now, when the therapeutic use of radioisotopes is surveyed again, we hope and expect that the answers to these questions will be available.

Radioactive phosphorus (^{32}P) has also been used successfully for the treatment of painful osseous metastases, primarily from carcinoma of the breast and prostate (54, 55). Useful palliation from severe and often intractable pain has been obtained in many cases. Relief from pain may be dramatic though the course of the disease remains unaltered. In some cases, however, radiographic and histologic evidence of healing of osseous lesions has been demonstrated while at the same time new lesions have appeared elsewhere. No effect on visceral or soft tissue metastases has been demonstrated.

Attempts to increase the efficacy of this form of treatment and to decrease the limitations imposed by ^{32}P induced bone marrow depression, by trying to invoke an osteoblastic response, have led to the use of ^{32}P in association with androgens (56) and following adrenalectomy (57). Tong and Rubinfeld have recently described yet another technique for increasing the localization of radiophosphorus in and immediately around metastatic osseous lesions (58). They have attempted to take advantage of the rebound effect leading to accelerated deposition of calcium and phosphorus in bone after withdrawal of exogenously administered parathyroid hormone. Pearson and his associates

(59), using calcium 47 and strontium 85 as tracers, have suggested that a differential uptake of greater than seven times normal may be necessary in order to obtain a beneficial therapeutic effect.

With the limitations imposed by the lack of therapeutically useful selective concentration after the systemic administration of radioisotopes in simple inorganic elemental form, a number of other methods have been ingeniously devised to localize isotopes by physical and/or mechanical means ("para-selective localization"). Suspensions of nonsoluble particles of radioisotopes, in the form of "radiocolloids" (60-62) have been widely used in intravascular, intracavitary, interstitial, and, most recently, in intralymphatic therapy. The radiocolloids of gold 198, phosphorus 32 as the chromic phosphate, and yttrium 90 have been used most extensively. The distribution, localization and concentration of these colloids depend upon the physical and to some extent upon the biological properties of the colloidal particles and not on the chemical nature or behavior of the particular radioactive element employed (60, 61).

After intravenous administration, radiocolloids are cleared rapidly from the blood and are deposited in the reticuloendothelial tissue of the liver, spleen, and to lesser extent, the bone marrow (63, 64). Although remissions have been obtained in the chronic leukemias (65, 66), polycythemia vera, and some cases of lymphoreticular malignancy (67), the usefulness of this form of therapy has remained rather limited.

Nonsoluble suspensions of even larger particles in the form of radioisotopes adsorbed onto carbon particles have been used by Muller (68) and others (69) in an attempt to localize radioactivity in the lungs after intravenous injection and in one lung or pulmonary segment after injection through a selectively placed cardiac catheter. Similarly, bismuth 206 adsorbed onto carbon particles has been administered intravenously in an attempt to obtain selective distribution and concentration in the treatment of lymphoreticular malignancies and chronic leukemia (70). These applications have remained largely experimental and do not promise anything more than limited clinical usefulness.

The principle of radioisotope localization by physical and mechanical processes after intravascular administration, however, as illustrated by these applications, has led to the development of another technique which promises to have greater therapeutic usefulness. Ceramic microspheres, with particle size in the range of 10 to 200 microns, and into which a wide variety of radioisotopes may be incorporated, have been developed recently (71) and have been investigated as a means of localizing radioactivity in the vascular bed of bulky tumors by intra-arterial or isolation-perfusion techniques (72, 73). The radioisotope(s) employed here, as in the colloidal and carbon particle techniques, acts solely as a radiation emitter, and is chosen on the basis of the suitability of its radiation spectrum and energies. Localization is accomplished by microembolization of the radiating microspheres into the vascular bed of the target organ or tumor after selective injection by means of

intra-arterial or isolation-perfusion techniques. Very dramatic tumor regressions have been obtained in this manner. The great advantage of this form of therapy over chemotherapeutic agents administered by these techniques is that the danger of "spill-over" into the systemic circulation with resultant bone marrow depression is obviated. This type of intravascular localization of radioisotopes presages a new area of usefulness for localized radiation therapy, as well as affords a useful method for the study of the vascular system.

INTRACAVITARY USE

The intracavitary injection of radioactive colloids has proven very useful for the control of malignant pleural and peritoneal effusions (62, 74). The radiocolloids of gold 198, chromic phosphate P 32 and yttrium 90 have been most commonly employed. The results using chromic phosphate P 32 and Y 90, which are both pure beta-emitters, have been comparable to those obtained using colloidal radiogold which emits both beta and penetrating gamma radiation. It would seem wiser and more prudent, then, to use the beta-emitters, thus obviating much of the radiation hazard and protection problem associated with the handling and administration of radiogold.

In our center as in many other medical centers, the intracavitary injection of any one of a number of chemotherapeutic agents (nitrogen mustard, thio-tepa, 5-fluorouracil, quinacrine) has supplanted the use of the radiocolloids as primary therapy for malignant effusions. The radiocolloids are reserved for instances in which a chemotherapeutic agent has failed to control the accumulation of peritoneal and/or pleural fluid.

In addition to their use for palliative treatment of malignant serous effusions, intracavitary radiocolloids have been administered prophylactically as an adjuvant to surgery in the treatment of carcinoma of the ovary (75-77). Elkins and Keettel (78) have demonstrated that a significant percentage of patients whose tumor is thought clinically to be limited to one ovary (Stage I disease) in fact have malignant cells in the peritoneal washings obtained at the time of surgery. Carcinoma of the ovary is well known for its propensity to metastasize widely throughout the peritoneal cavity in many cases considered "favorable" or surgically curable on the basis of finding localized disease at the time of surgery. It thus seems reasonable to suspect that some of these recurrences, at least, may be due to the presence of free cells and/or microscopic peritoneal implants that result from spontaneous shedding of malignant cells into the peritoneal cavity or as a result of operative trauma. The prophylactic adjuvant use of colloidal radiogold, in combination with conventional surgical therapy, is being explored at a number of institutions (75-77) in an attempt to increase the cure rate in early ovarian carcinoma. The results thus far have been encouraging, though figures to prove the effectiveness of this form of therapy are not yet available. Carefully controlled clinical trials will hopefully prove or disprove the practical value of this theoretically sound idea.

INTERSTITIAL USE

Numerous isotopes, in a variety of chemical and physical forms, have been used for interstitial injection therapy. Again, the radiocolloids of gold 198, chromic phosphate (P 32), and yttrium 90 have been used most extensively for this purpose. In these applications, the inert and insoluble radioactive particles are physically localized by direct injection into the target tissue or tumor. By virtue of the physical properties and chemical inertness of the radiating sources used, they tend to remain localized to the site of injection and to the regional lymphatics and lymph nodes draining the area.

Direct intratumoral injection has been applied in this manner to the treatment of selected cases of prostatic carcinoma (79, 80). Radiocolloids have also been injected transvaginally into the parametria in an attempt to sterilize possible micrometastases in the parametrial and lateral pelvic lymph nodes in cases of carcinoma of the uterine cervix (81-83). Intraparametrial colloidal gold has also been used with some success in the treatment of intractable pelvic pain associated with widespread pelvic metastases from carcinoma of the cervix (84, 85). In addition, attempts to radiate the regional lymph nodes in cases of carcinoma of the breast following intra-mammary interstitial injections of radiocolloidal gold 198 have been reported (86, 87).

The results of interstitial therapy have been satisfactory in some cases (80, 82, 84, 85) but disappointing in others (88, 89). The usefulness of this form of therapy is limited by the technical and physical problems of accurate isotope placement and by the inadequate localization and uneven distribution attained in many cases. Furthermore, foci of metastatic tumor within lymph nodes do not pick up and concentrate the colloid to any degree (90, 91). Because of the very limited range of the beta radiation, cancerocidal doses of radiation cannot be expected to reach metastatic deposits exceeding a few millimeters in size.

INTRALYMPHATIC USE

A new approach to lymph node irradiation, utilizing the technique of lymphangiography, has been reported recently (92-95). The direct intralymphatic injection of therapeutic amounts of colloidal radioactive gold 198, chromic phosphate (P 32), or radioiodinated oily contrast material (ethiodol, lipiodol) has been used to distribute cancerocidal radiation doses to retroperitoneal and other lymph nodes in cases of lymphoreticular malignancy and carcinoma. With satisfactory distribution, concentration and retention of the radioactive materials dramatic responses may be obtained (95, 96).

Intralymphatic radioisotope therapy has also been used prophylactically in an attempt to sterilize the regional lymph node drainage in cases of carcinoma of the uterine cervix (94, 97), testicular tumors (98, 99), malignant melanoma (100), and other malignancies (101). The ultimate usefulness of this mode of therapy remains to be proved. It would seem to have its greatest potential

in the area of prophylactic adjuvant therapy where it offers the hope of destroying lymphatic micrometastases that arise spontaneously or as a result of operative trauma. The Medical Research Council of the United Kingdom has taken a forward step in this area and is planning to undertake a large scale controlled clinical trial of intralymphatic radioisotope therapy in cases of potentially curable malignant melanoma of the extremities (102). These results, and those of other well-planned, controlled clinical trials will ultimately establish the place of this mode of radioisotope therapy in our armamentarium.

QUO VADIS?

Finally, there are a number of therapeutic applications that are still largely experimental or developmental, but which promise potential future clinical usefulness and which suggest future trends in the therapeutic use of radioisotopes.

Radiocolloidal gold 198 may be administered intra-articularly in the treatment of chronic recurrent synovial effusions. Very satisfactory and encouraging results have been obtained in a limited number of patients with a variety of articular disorders wherein other methods have failed (103, 104).

The stable isotope of an element with a large cross section area for neutron capture may be made radioactive *in situ* by bombardment with thermal or epithermal neutrons from a nuclear reactor. Stable boron 10, when administered systemically in suitable chemical form, is concentrated to some degree within certain central nervous system tumors, compared to the surrounding normal nervous tissue. When bombarded with thermal neutrons, as in "neutron capture therapy," the stable boron 10 gives rise to a high energy alpha particle and a lithium atom. Because of the high kinetic energy and very limited range of the alpha particles produced, an intense ionization path is produced locally over an area that may not exceed the size of a single cell. This form of therapy has been applied in the treatment of glioblastoma multiforme and other malignant intracranial tumors (105-107). Neutron capture therapy remains an experimental form of treatment; because of the many complicated physical and technical problems involved and the requirement for a nuclear reactor, it will probably remain of rather limited practical usefulness.

Another recent therapeutic application has been the use of very short-lived radioisotopes in the therapy of malignant tumors by isolation-perfusion technique (108, 109). Scandium 49, zinc 69, and dysprosium 165, all beta-emitters, have been utilized as sources of short-lived intense beta radiation, their short half-lives serving to reduce the hazards associated with any leakage that may occur into the systemic circulation.

A number of different methods, including radioisotope techniques, have been investigated in an attempt to modify the homograft reaction by inducing lymphocytopenia and immunosuppression. Acute and chronic beta irradiation of the circulating blood has been achieved experimentally *in vivo*

by the use of a yttrium 90 source implanted into (110, 111) or surrounding (112) a segment of the abdominal aorta, or suspended in the right atrium (113). These methods, though still largely experimental, promise possible future clinical usefulness in the developing field of transplantation immunology.

Ingenious attempts have been made to achieve selective localization of internally administered radioisotopes by the use of chelating agents. Yttrium 90 chelated to diethylene triamine penta-acetic acid (DTPA) has been used with some success by Winchell and associates at the Donner Laboratory to achieve a certain degree of selective lymphoid radiation, and has been applied to the induction of lymphocytopenia and immunosuppression (114, 115). Greenberg and associates (116, 117) have reported preliminary results of the treatment of multiple myeloma and polycythemia vera with another yttrium 90 chelate that is relatively selectively deposited in bone and bone marrow.

Similarly, investigations have been undertaken into the therapeutic use of radioactive drugs (118), antibodies (119, 120), and even essential body metabolites (121). These techniques represent still further attempts to overcome the problem of selective localization, which remains the major obstacle to the wider and more successful use of internally administered radioisotopes for therapy.

Though it is apparent that few truly significant "breakthroughs" have as yet occurred in radioisotope therapy, the nuclear radiations of a variety of isotopes, used in numerous forms and administered in a number of different ways, have been very successfully applied to the palliation and occasional cure of both neoplastic and non-neoplastic human disease. The development of significant new therapeutic advances in the field of radioisotope therapy, as in cancer therapy in general, must await further extension and expansion of our knowledge of the nature and natural history of the malignant process itself.

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CLINICO-PATHOLOGICAL CONFERENCE

Pancytopenia and Chronic Pulmonary Disease in an Elderly Male

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An 83 year old white man was admitted to The Mount Sinai Hospital for epistaxis.

The patient had chronic bronchitis and emphysema for many years. Six years earlier he was hospitalized for bronchopneumonia and rupture of the rectus muscle secondary to an episode of coughing. He remained well except for a chronic cough until 16 months prior to admission when he developed shortness of breath and signs of congestive heart failure. On admission the hemoglobin was 6.5 gm/100 cc, the white blood cell count 4,425/cu mm with 29% polymorphonuclear leukocytes, 2% band forms, 67% lymphocytes, 1% eosinophils, and 1% monocytes. The erythrocyte sedimentation rate was 137 mm/hour and reticulocyte count was 1.1%. A peripheral smear showed moderate hypochromia. The BUN was 42 mg/100 cc and the blood glucose 110 mg/100 cc. The serum bilirubin, electrolytes, cholesterol and alkaline phosphatase activity were normal. Several stools were strongly guaiac positive. An x-ray film of the chest was normal. A barium enema demonstrated a large number of diverticula in the right colon, and an upper gastrointestinal series showed a small sliding hiatus hernia and spasticity of the duodenal bulb. The bone marrow was hypocellular, with a marked increase in lymphocytes and mast cells. He improved with antibiotics, bronchodilators, diuretics and several units of packed cells.

Because of recurrent dyspnea he was readmitted one month later. The blood pressure was 140/80, pulse 100/min, respirations 32/min, and temperature 101.4°F. The sclerae were slightly icteric. The neck veins were distended, and hepatojugular reflux was elicited. The anterior-posterior diameter of the chest was increased and crepitant rales and expiratory wheezes were heard bilaterally. The heart was normal. The liver was palpated three fingerbreadths below the right costal margin. The spleen was not felt. Clubbing or edema was not present. The hemoglobin was 5.3 gm/100 cc, the white blood count 3,000/cu mm with 22% segmented leukocytes, 9% band forms, 60% lymphocytes, 2% eosinophils, 1% basophils and 2% monocytes. The reticulocyte count was 3.7%, and the platelet count 60,000/cu mm. The peripheral blood smear again showed moderate hypochromia and marked rouleaux formation. The blood uric acid was 6.4 mg/100 cc, serum albumin 1.8 gm/100 cc and globulin 5.8 gm/100 cc. Electrophoresis of the serum demonstrated a slow gamma spike. A Sia test was

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positive. The serum viscosity was 2.7 (normal 1.5). A Coombs' test was negative. The serum B₁₂ was normal and the serum folate level was elevated. The serum iron was 94 $\mu\text{g}/100\text{ cc}$, and the total iron binding capacity was 225 $\mu\text{g}/100\text{ cc}$. A chest x-ray was unchanged, and the electrocardiogram showed a RSR pattern in V₁.

He was treated with multiple transfusions and antibiotics, but he remained febrile with temperature elevations to 101°F. Blood and urine cultures were sterile. Chlorambucil, 0.1 mg/kg/day was instituted. Two days later the white blood count was 2,100/cu mm and the hemoglobin was 9.5 gm/100 cc.

He was discharged to be followed by his private physician. However, a severe episode of epistaxis required readmission six days later. The physical examination was unchanged except for multiple perianal abscesses. The hemoglobin was 10.7 gm/100 cc, white blood cell count 2,350/cu mm and platelet count 84,000/cu mm. The serum albumin was 3.11 gm/100 cc, alpha₁ globulin 0.27 gm/100 cc, alpha₂ 0.46 gm/100 cc, beta 0.36 gm/100 cc and gamma 4.0 gm/100 cc.

Digoxin, oxacillin, and bronchodilator therapy was continued. Shortly after admission he attempted suicide and was transferred to the psychiatric unit. Pancytopenia persisted although the patient had not received chlorambucil for over one month. He received two units of packed red cells. Allopurinol therapy was instituted because of an elevated uric acid, and plasmapheresis was performed. The hematocrit was 30. On the 45th hospital day his temperature rose to 103°F. The blood pressure was 80/60. Rales were heard bilaterally and an x-ray film of the chest showed an infiltration in the midportion of the left lung. Despite vigorous antibiotic therapy, he died the following day.

*Dr. Nathaniel Wisch**: This 83 year old man presented with a disease which became manifest 17 months prior to his death. His first admission to The Mount Sinai Hospital was prompted by signs and symptoms of congestive heart failure. He had an anemia and a mild leukopenia with a relative lymphocytosis. No abnormal white cells were noted on peripheral smear, and the red cells showed a moderate hypochromia. There was no significant reticulocytosis and his sedimentation rate was 137 mm/hour. His urine contained 1 plus protein. The BUN was 42 mg/100 cc, and all of the other blood chemistries were normal. On several occasions, he had strongly positive stool guaiacs and x-ray films of the gastrointestinal tract revealed a small hiatus hernia, spasticity of the duodenal bulb, and diverticulosis of the colon. A bone marrow determination showed increased number of mature lymphocytes, plasmacytoid lymphocytes, reticulum cells, mast cells, and marked reduction of megakaryocytes, and erythroid and granulocytic precursors (Fig 1).

He was treated for congestive heart failure and anemia with transfusions of red cells. Fifteen months later he was readmitted with congestive heart failure and fever. A large liver was noted and he was icteric. The pancytopenia was more profound, the white blood count was 3,000/cu mm with a relative

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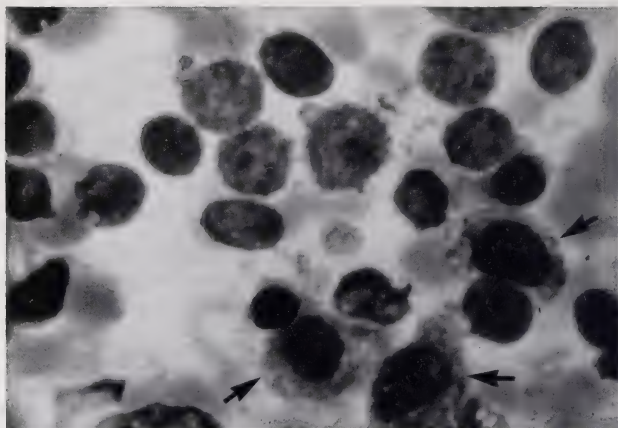


Fig. 1. Bone marrow showing lymphocytes and plasmacytoid lymphocytes (arrows) (Giemsa $\times 960$).

lymphocytosis, and his platelet count was 60,000/cu mm. The red cells were moderately hypochromic with marked rouleaux formation and there was a mild reticulocytosis. His uric acid was 6.4 mg/100 cc, and the serum albumin was low and the globulin elevated. Paper electrophoresis of the serum showed a slow gamma spike. This was the first indication that the patient had a protein abnormality, aside from the elevated sedimentation rate. Generally speaking, a serum protein spike suggests certain diseases, especially multiple myeloma. However, lymphoproliferative diseases and other malignancies also are associated with abnormal elevations of serum proteins. A Sia test was positive. Although the Sia test is a useful screening test for the presence of macroglobulins, it is by no means conclusive. It indicates that the patient has a serum protein which precipitates in electrolyte-free water. Further studies should be performed to definitely establish the presence of macroglobulins. Starch gel electrophoresis is valuable. Since macroglobulins do not migrate on a starch media a spike on paper electrophoresis that cannot be demonstrated on a starch media, suggests the presence of a macroglobulin. Immunoelectrophoresis is more specific. However, ultracentrifugation is the only conclusive method of demonstrating the presence of a macroglobulin.

He had slight proteinuria but a Bence-Jones protein was not found. The patient had a serum viscosity of 2.7, the normal being 1.5. If the viscosity was measured at 37°C, it was not clinically significant. Usually, symptoms result when the viscosity is six to eight times normal. However, recent studies

have indicated that certain macroglobulins show higher viscosities at lower temperatures and I cannot exclude the presence of an increased viscosity unless the viscosity studies were performed at lower temperatures also.

The Coombs' test was negative, the serum B₁₂ was normal, and the serum folic acid was elevated. The latter may have resulted from vitamin therapy and was not pertinent to the patient's disease. The serum iron and total iron binding capacity were normal, and the ECG showed a RSR₁ pattern in V₁, probably secondary to his chronic lung disease. He was treated with blood transfusions, antibiotics and chlorambucil. Apparently within a period of 48 hours, the white blood count fell from 3,000 to 2,100 and therapy was stopped. I doubt that the drop in the white count was due to the drug therapy.

He was then discharged only to be readmitted six days later with epistaxis. The hemoglobin was mildly reduced and the leukopenia and thrombocytopenia persisted. What caused the epistaxis? Certainly, patients with moderately reduced platelets do not usually manifest significant bleeding, and a local lesion was not mentioned in the protocol. In patients with dysproteinemias and more specifically with macroglobulinemias, several of the coagulation factors are absorbed onto the abnormal protein, and bleeding may result from ineffective clot formation. I think this was the case. Abnormalities in bleeding, secondary to the abnormal proteins, can usually be corrected by vigorous plasmapheresis or some form of therapy which will break up the abnormal protein, such as penicillamine. Occasionally, steroid therapy is effective. The patient apparently attempted suicide which may be significant in that psychiatric problems have been reported in various dysproteinemias, particularly in patients with macroglobulinemia.

In summary, this elderly man had a pancytopenia, gastrointestinal as well as nasal bleeding, a protein spike on paper electrophoresis, a positive Sia test and congestive heart failure, secondary to a severe anemia. Multiple abscesses developed during his 17-month course, and he finally died with a bronchopneumonia.

The bone marrow showed infiltration of mature lymphocytes, plasmacytoid lymphocytes, and mast cells. The protein spike on electrophoresis suggested multiple myeloma. Certainly the peripheral blood picture and pancytopenia is consistent with multiple myeloma as is an increased incidence of infection and bleeding tendency. However, the patient did not have bone lesions nor the typical bone marrow abnormalities. It is true that many patients with myeloma do not always show the typical bone marrow findings, but this patient had a definitely abnormal marrow not typical of multiple myeloma. In addition, mast cells have rarely been reported in multiple myeloma. He did have protein in his urine and Bence-Jones protein was sought but was not detected.

Chronic lymphatic leukemia has been reported to produce spikes on electrophoresis, but because of the lack of leukocytosis, I think we can exclude this diagnosis. Patients with lymphosarcoma can present with pancytopenia, and may not have peripheral adenopathy, splenomegaly or hepatomegaly. However, mast cells in the bone marrow and protein spikes have rarely been

reported. Reticulum cell sarcoma is also possible. However, the cells in the marrow were more mature than one usually finds in reticulum cell sarcoma. Isolated carcinomas have been reported to give protein spikes and pancytopenia, but when the marrow is invaded with tumor cells, the diagnosis is obvious. Finally, Waldenström's macroglobulinemia is a relatively rare condition, characterized by the formation of an abnormal protein of a large molecular weight, associated with the proliferation of lymphocytes and plasma cells, and frequently mast cells. Clinically, these patients complain of weakness and lethargy, associated with anemia. Infections are common though not necessarily because of the low white count, but because their normal immunoglobulins are significantly reduced, even if they have a marked increase in gamma globulin. Lymphadenopathy occurs, but only in about 30 or 40 percent of the cases. This patient did not have any significant lymphadenopathy. Splenomegaly and hepatomegaly occur but also in less than half the patients, and Bence-Jones protein is present in approximately 10 to 20 percent of the cases. The white count is usually normal, but may be low. The common clinical features that these patients have are due to the increased viscosity of the blood and are manifested by bizarre neurologic complaints, eye ground abnormalities which are due to precipitation of the abnormal protein in the small blood vessels of the retina and lymphatic spaces in the brain. This patient's blood viscosity was not high enough to account for symptoms related to hyperviscosity, and usually patients do not have problems until the viscosity is six times greater than normal.

Amyloidosis occurs secondary to macroglobulinemia. In reviewing the literature, I was able to find 12 cases reported. In myeloma, amyloidosis has been reported most frequently in those patients who have Bence-Jones protein either in the urine or in the serum. However, in patients with macroglobulinemia, only one out of the 12 cases have Bence-Jones protein. I doubt very much whether this patient had amyloid disease, since he lacked splenomegaly. He did not have skin changes nor neurologic deficits, and no evidence of the nephrotic syndrome or gastrointestinal tract abnormalities. He developed congestive failure, but I think this was secondary to the anemia. Since infections are prevalent in patients with lymphoproliferative disease and macroglobulinemia, one always has to consider a fungal infection or tuberculosis. However, there was no clinical evidence of a superimposed infection.

In summary, I think this patient had Waldenström's macroglobulinemia. His anemia was secondary to gastrointestinal bleeding and ineffective erythropoiesis due to invasion of the bone marrow. The bleeding abnormality was probably secondary to the abnormal serum protein. He had chronic lung disease and died of a bronchopneumonia. Incidentally, he had a hiatus hernia and diverticulosis of the colon, either of which could have produced gastrointestinal bleeding. I might add that therapy in macroglobulinemia is difficult. Plasmapheresis has been attempted in patients with hyperviscosity, with severe bleeding, and can be rather effective. Steroids are also sometimes of value. Penicillamine and other agents which will break up the abnormal pro-

tein have been used, and have been effective only occasionally. Gamma globulin, of course, can be used to tide these patients over an infectious process, since they are susceptible to infections more readily than most patients, and it is usually due to the fact that their normal immunoglobulins are greatly reduced.

As far as chemotherapy is concerned, probably the most effective agent is chlorambucil, and it was tried with this patient but discontinued after 48 hours because of the significant drop in his white count.

This drug really does not have any significant effect for several weeks or even months. It acts by decreasing the activity of the cells that are producing the abnormal protein. Therapy in this disease is limited and not particularly effective.

I might add that this disease is characterized by two forms. In the more chronic form the patients have a protracted course usually lasting four or five years. Other patients have a more acute form than this patient. Why one patient has a more prolonged course than another is unknown. There are no differences in the protein abnormality or the histology of the bone marrow.

Are there any questions?

Speaker from the Audience: You mentioned cases of tuberculosis associated with pancytopenia which are not diagnosed until autopsy.

Dr. Wisch: The bone marrows of patients with tuberculosis are usually hypoplastic or even aplastic. This patient's marrow was hypercellular and the infiltration of lymphocytes and plasmacytoid lymphocytes is not typical of hematogenous tuberculosis. Most often the bone marrow shows an increase in lymphocytes or exclusively lymphocytes.

Dr. Geller:* Thank you, Dr. Wisch.

At autopsy, the body was that of a well developed, slightly malnourished elderly white male. The lungs were hyperaerated and showed evidence of bronchitis.

The liver, because of the hyperexpanded right lung, extended 14 cm below the right costal margin in the midclavicular line, and 10 cm below the xyphoid.

The spleen was large but was subcostal.

The heart was slightly enlarged and there was moderate left ventricular hypertrophy. There were scattered foci of myocardial fibrosis, but no evidence of infarction. The coronary arteries and aorta showed moderate to severe atherosclerotic changes with small foci of calcification.

The prostate was enlarged and there was compensatory trabeculation of the bladder.

The thyroid contained a 3 cm benign adenoma.

The adrenals weighed two and six times normal, and showed mottled hemorrhagic, necrotic, adenomatous areas. The central vein of the adrenal was thrombosed bilaterally.

In addition, two pedunculated adenomatous polyps were found in the sigmoid colon.

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The bronchial cartilage contained many areas of osseous transformation, with foci of hematopoiesis.

The bone marrow within the bronchial cartilage was hypercellular, composed largely of lymphocytoid or plasmacytoid cells, that is, cells intermediate between lymphocytes and plasma cells. These cells were found throughout the body as irregular, pleomorphic infiltrates invading the wall of the stomach, the small intestine, within the kidneys, and between the atrophic, hyalinized seminiferous tubules of the testes.

The liver was moderately enlarged, and was firm and brown in color. The portal tracts were accentuated by a cellular infiltrate, and the central areas were congested.

An iron stain showed marked deposition of hemosiderin, evidence of erythrophagocytosis, and scattered foci of extramedullary hematopoiesis.

In addition, there were many plasmacytoid cells with intracytoplasmic accumulations of PAS-positive, glycogen-rich material.

The spleen was four to five times its usual weight. On section it was brown, congested and soft. There were small foci of necrosis as well as plasmacytoid or lymphocytoid cell infiltrations, and some extramedullary hematopoiesis.

The lymph nodes were slightly enlarged throughout the body and were markedly congested. The normal lymphoid architecture was distorted by proliferation of transitional cells and some mast cells. Some of the transitional cells contained accumulations of PAS-positive material.

The vertebral bodies and other bones examined were intact.

Microscopically, there was evidence of osteoporosis. The bone marrow was hypercellular and consisted of intermediate cells, a few megakaryocytes, and mast cells. Erythroid precursors were decreased. In addition, many cells were found with intranuclear PAS-positive inclusions (Fig 2).

As Dr. Wisch correctly surmised, this patient had Waldenström's macroglobulinemia.

In 1960, Dutcher and Fahey (1) postulated that PAS-positive material was transferred from the nucleus into the cytoplasm and eventually extruded from the cell into the plasma. The crystalline, protein-like nature of this material has now been demonstrated with the electron microscope and shown to be macroglobulin by immunofluorescent and cytochemical techniques (2).

Zucker-Franklin et al (3), in 1962, performed an elegant *in vitro* study in which they cultured the plasmacytoid cells of lymph nodes biopsied from patients with Waldenström's macroglobulinemia, and demonstrated that the abnormal transitional cells have the ability to incorporate a radioactive amino acid from the tissue culture media into macroglobulins and secrete them into the media.

Histologic examination in this patient showed many cells bursting with this glycogen-rich material, presumably macroglobulin about to be extruded. Although the intranuclear accumulation of PAS-positive material has been reported in one case of myeloma, it is almost pathognomonic of Waldenström's macroglobulinemia. The inclusion reported in myeloma was morphologically

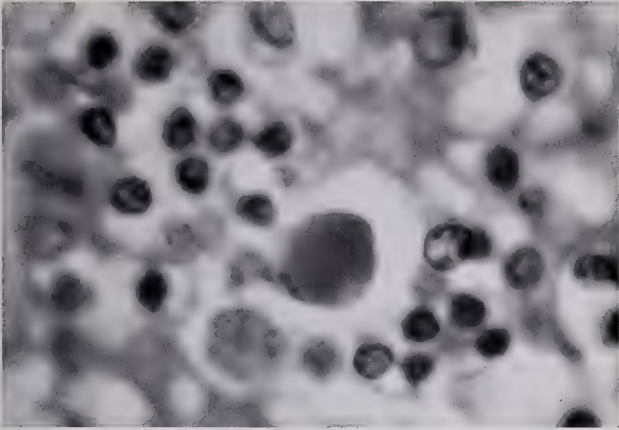


FIG. 2. Bone marrow with a plasmacytoid cell containing internuclear PAS-positive material (PAS \times 960).

similar to macroglobulin, but could be distinguished chemically. Normally, 5 to 10 percent of the serum proteins are macroglobulins. Levels greater than 15 percent are strongly suggestive, and levels greater than 20 percent are pathognomonic of this disease.

Ultracentrifugation of the plasma proteins performed in this case showed levels greater than 27 percent.

Epistaxis in an elderly male is the classic mode of presentation and may be the result of thrombocytopenia, defective clot formation secondary to dysproteinemia, or due to direct infiltration of mucous membranes by abnormal cells. The macroglobulin results in a high blood viscosity with concomitant sludging of blood, and this may also contribute to the bleeding. Furthermore, fluorescent antibody studies have shown that both the red cells and platelets become coated with macroglobulin. This alters their biochemical and biophysical state and leads to increased erythrophagocytosis and iron deposition. Coating of platelets may interfere with their disintegration and liberation of platelet clotting factors. Of course, the anemia, leukopenia and thrombocytopenia are largely due to replacement of the marrow by abnormal cells.

Decreased red cell survival due to bleeding, hemolysis and hypersplenism may be a factor also, and iron deficiency may contribute to the anemia.

Jaundice has been reported in association with Waldenström's macroglobulinemia, and a recent report described a transient episode of jaundice reminiscent of the present case (4).

Dr. Popper and co-workers (5) described a case of subacute hepatitis associated with this disease, in which macroglobulins were identified in the inflammatory cells.

The etiology of the jaundice in our case is not clear, but is probably due to both congestion of the liver and infiltration with abnormal cells.

Renal failure, which is so common in myeloma, is quite rare in this condition, and in this case there was insufficient infiltration of abnormal cells to cause renal failure. Congestion may have been a factor.

Brain infiltrations are rather common and produce both psychiatric and neurological manifestations.

Mast cells were first described by VonRecklinghausen a little over 100 years ago, but it remained until 1878 for Paul Ehrlich to include a rather complete description of them in his doctoral thesis. He named them "Mastzellen" because he believed the granules were due to over-feeding by the cells. The mast cells have been shown to contain heparin, histamine, hyaluronic acid, serotonin and many enzymes. The role of mast cells in Waldenström's macroglobulinemia is unclear, but they have been described in 10 to 20 percent of the cases, and frequently have been incriminated as the cause of the hemorrhagic tendency because of their heparin content. Mast cells also have been described in a multitude of infectious, neoplastic, toxic, and metabolic diseases.

The etiology of this disease is uncertain and Waldenström himself has been widely misquoted as having postulated a viral etiology in his original description of the disease. He has recently refuted this, noting that he merely compared the abnormal protein production with a phenomenon occurring in plants infected with virus particles (6).

It seems likely that a somatic mutation occurs in a single clone of plasma cells which begin to produce the abnormal quantities of macroglobulin. In the past few years, many workers have reported an abnormal, large 47th chromosome in lymphocytes cultured from patients with this disease (7). The relationship of this abnormality to the disease, however, is not clear. It is interesting to note that one recent paper found a decreasing frequency of the abnormal chromosomes after the patients were treated (8). Abnormal chromosomes also have been found in some relatives of these patients.

Waldenström has recently questioned the direct relationship of malignancy to macroglobulinemia, but commented upon the association of tumors in 10 to 15 percent of the cases (9). This case represents one example. The right kidney was slightly enlarged and there was a 4 to 6 cm mass on the anterior aspect of the upper pole (Fig 3). It was yellow, with central necrosis and hemorrhage, and microscopically was a clear cell hypernephroma with focal invasion of the capsule, but no evidence of local or distant metastases. Finally, throughout the large intestine, we found abnormal accumulations of brownish pigment in the submucosa consistent with melanosis or pseudomelanosis coli. This pigment is evidence of chronic cascara abuse, and the rectum showed evidence of longstanding mucosal ulceration.



FIG. 3. Large hypernephroma in the upper pole of the right kidney.



FIG. 4. Area of septic infarction within the right lung.

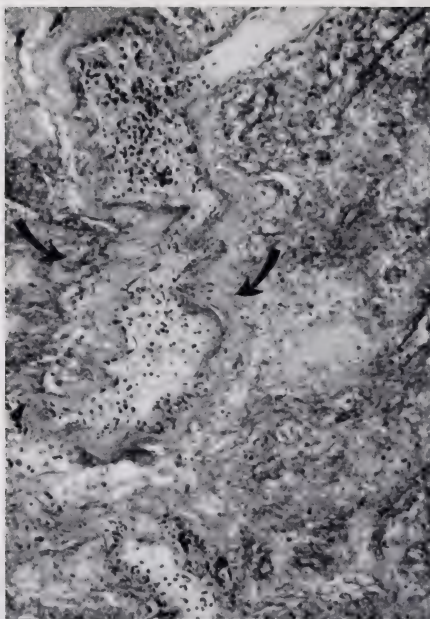


FIG. 5. Microscopic section of lung in zone of septic infarction showing thrombosed pulmonary vein (arrows) (H&E $\times 540$).

Microscopically, in the areas of necrosis, the veins were thrombosed, and large numbers of gram-negative rods, resembling *B. pyocyaneus* were seen.

The lungs were congested, edematous, boggy, and showed large areas of septic infarction (Fig 4).

Microscopically, there was necrosis, venous thrombosis, and numerous gram-negative rods, and absence of an inflammatory reaction characteristic of pseudomonas infections (Fig 5).

Patients with macroglobulinemia produce an immunologically deficient globulin which impairs antibody responses. In the present case, because of the decreased resistance and impaired antibody production, repeated rectal infections probably led to septic emboli, and the patient died with septic pulmonary infarcts.

Final Diagnoses:

1. Waldenström's macroglobulinemia
2. Hypernephroma of the right kidney

3. Acute and chronic proctitis
4. Bilateral septic pulmonary emboli with infarction
5. Adenomas of thyroid and adrenal gland
6. Arteriosclerotic heart disease
7. Chronic bronchitis and emphysema

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RADIOLOGICAL NOTES

CLAUDE BLOCH, M.D. AND HARVEY M. PECK, M.D.

CASE NO. 295

A two year old boy was admitted to the hospital with acute onset of difficulty in breathing. There was no antecedent coryza or fever and the patient's parents denied any history of aspiration. Chest x-ray films in the frontal projection revealed no pulmonary infiltrations or pleural effusions. A peculiar faint radio-paque density was noted overlying the upper portion of the trachea on the chest roentgenogram (Fig 1A, (*arrow*)). For this reason an examination of the cervical region was performed using Bucky technique. A thin linear calcific density was then clearly visible to the left of the midline within the mid-portion of the tracheal air contour (Fig 1B). Endoscopy was immediately performed and a 3 cm long friable foreign body was dislodged from the subglottic region. This turned out to be an intact segment of an eggshell. The patient made an uneventful recovery. On more careful and pointed questioning, a history of the aspiration episode became evident.

DISCUSSION

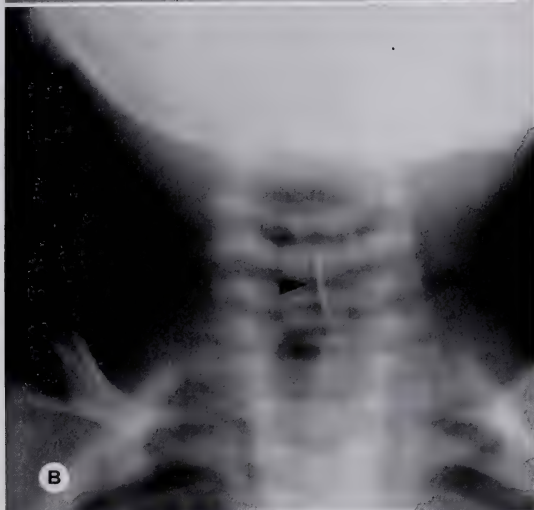
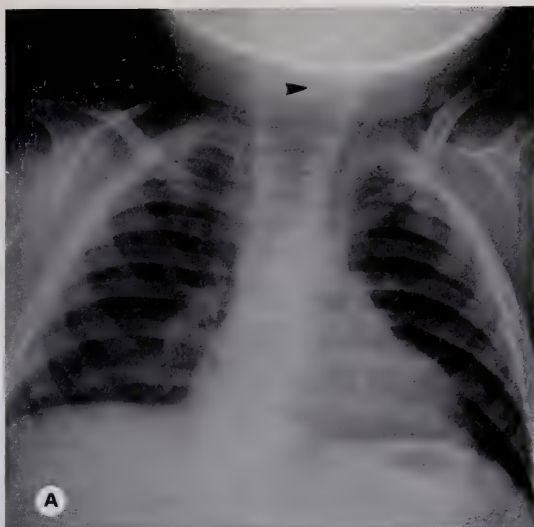
This case points to the importance of careful scrutiny of all portions of the chest roentgenogram in cases of severe respiratory embarrassment. Aspirated foreign bodies are often radiolucent and only detectable by their indirect effects such as atelectasis and obstructive emphysema. In the case presented, it would have been easy to overlook the thin eggshell calcification, not only because of its faint outline, but also because of its unusual location on the upper border of the x-ray film itself. A Bucky examination with proper centering and coning made the opaque foreign body evident.

—Claude Bloch

Case Report: EGGSHELL FOREIGN BODY IN SUBGLOTTIC REGION EVIDENT ON CHEST ROENTGENOGRAM.

Acknowledgment: The editors wish to thank Dr. Max L. Som for permission to publish this case.

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Case 295, Fig. 1A. There is a peculiar faint linear radiopaque density overlying the upper portion of the trachea as seen on this posteroanterior view of the chest (arrow).

Case 295, Fig. 1B. A Bucky film of cervical region confirms the presence of the curvilinear density just to the left of the midline within the subglottic region (arrow). This corresponded to the large segment of eggshell found at endoscopy.

CASE NO. 296

A ten month old female was in apparent good health until one week prior to hospitalization, when she developed fever and malaise. On examination, bilateral large abdominal masses were palpated and the patient was immediately hospitalized. General physical examination revealed a robust child in no distress. Positive findings were limited to the abdomen, where two large firm non-tender masses filled the epigastrium and could be palpated within the flanks. Laboratory examination revealed a normal hemogram and sedimentation rate. Skeletal series and chest x-ray films were normal. An intravenous pyelogram showed marked enlargement of the renal outlines, more marked on the left side. There was severe distortion of the calyces which were indented by multiple nodular masses (Fig 1A). In the lateral projection, the masses were noted to be predominantly situated anteriorly with posterior splaying of the calyces and pelves (Fig 1B). A diagnosis of bilateral Wilms' tumors was made and a preoperative course of Cobalt-60 radiotherapy was given. A mid-plane tumor dose of 750 rads was administered via apposing 14 x 17 cm fields in a three week period. The patient was also given a course of Actinomycin D and vinceristine. Surgery was then performed and a large nodular mass was noted to involve the entire left kidney. No surgical procedure was possible on that side. On the right side a partial nephrectomy was performed in an attempt to remove the tumor. Postoperative radiotherapy and continued antitumor chemotherapy were also given.

DISCUSSION

Wilms' tumors are characteristically unilateral in location and represent one of the most frequent tumors of childhood. When they occur bilaterally, the problem of a roentgen differential diagnosis becomes important. Neuroblastomas may produce indentations and deformities on both collecting systems. Also the possibility of multiple benign renal cysts must be taken into account. In neuroblastomas, abnormal calcifications are frequently encountered within the tumor masses. In the case presented, the tumor on the left side involved the entire kidney and was unresectable. On the right side, a partial nephrectomy was performed with removal of the entire gross neoplasm.

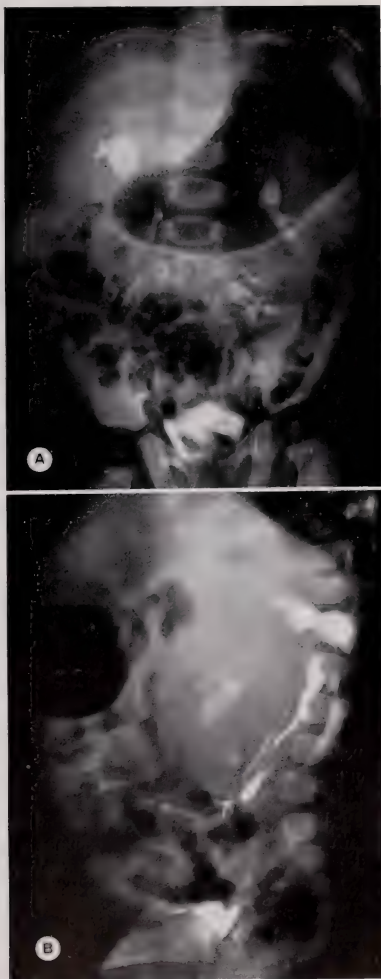
—Claude Bloch

Case Report: BILATERAL WILMS' TUMORS.

Acknowledgment: The editors wish to thank Drs. John Boland, Horace L. Hodes, and Samuel Andelman for permission to publish this case.

Case 296, Fig. 1A. Supine film of abdomen during the course of an intravenous pyelogram reveals marked distortion and "splaying" of the calyces of both kidneys. The renal outlines are markedly enlarged especially on the left side. Large nodular masses indent the pelves bilaterally.

Case 296, Fig. 1B. In the lateral projection, the main portion of the tumor mass is noted to be situated anteriorly with bilateral posterior displacement of the calyces and renal pelves.



CASE NO. 297

A 67 year old female underwent a resection for a jejunal myosarcoma in 1943. The patient was asymptomatic until 1965, when she noted the onset of abdominal pains. Soon afterward, a left upper quadrant mass became palpable and x-ray films of the small bowel demonstrated an 8 x 5 cm mass closely related to the proximal jejunum and adjacent to the greater curvature of the stomach. No mucosal abnormalities or point of attachment were noted. At operation, a well circumscribed tumor was found attached to the first jejunal loop beyond the ligament of Treitz. A small segment of jejunum was resected with the lesion, and an end-to-end jejunojejunostomy was performed. The specimen revealed myosarcoma. The patient was well until 1967, when she again developed a palpable firm smooth tender mass to the left of the umbilicus. Small bowel series which had been normal in December, 1966, revealed a mass attached to the proximal jejunum (Fig 1A). The involved loop showed a constant flattening and "pleating" of the mucosal folds, but no ulceration (arrow). A number of additional jejunal and proximal ileal loops were also involved (Fig 1B) with some evidence of fixation of the involved segments, some angulation, but no dilatation or signs of intestinal obstruction. Barium enema revealed that one of the masses caused a contour defect upon the sigmoid colon (Fig 2, *arrow*). At surgery, numerous masses were identified invading the jejunum and mesentery. Innumerable small serosal implants were also noted. The large masses were removed and the patient made an uneventful recovery. She was then placed on antitumor chemotherapeutic agents.

DISCUSSION

This case underseores the frequent long-term survival and protracted course of patients with isolated small bowel myosarcoma. These tumors may often recur in a localized fashion within the small bowel and still be locally resectable; eventually they almost invariably become generalized within the peritoneal cavity. From a roentgen point of view, when localized, these tumors present as typical submucosal lesions, but their point of attachment to the bowel is often difficult to demonstrate. They often appear to represent benign tumors both roentgenographically and on the gross and even microscopic pathological study. Only few mitoses are seen and their natural history is that of a slow growing tumor of low grade malignancy. All that is noted is often a subtle distortion of the mucosal folds and some angulation of the involved loop. In their more aggressive form, small bowel myosarcomas are easily recognized with large irregular ulcerating nodular masses often causing no signs of intestinal obstruction. When the peritoneal cavity is studded with tumor metastases, numerous nodular lesions are then seen which fix the intestinal loops as in the cases presented above.

—Claude Bloch

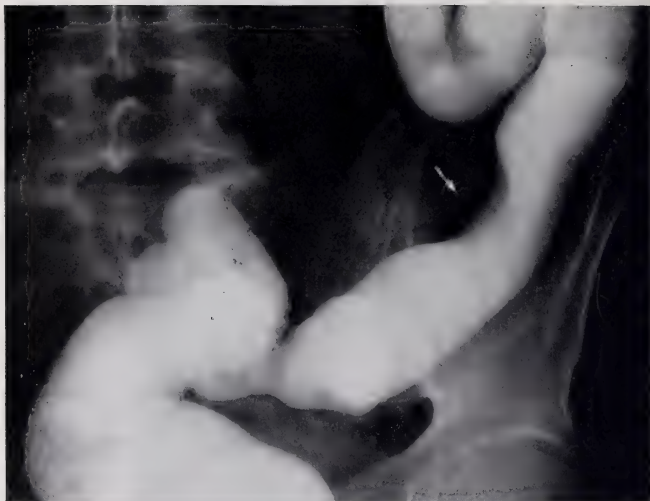
Case Report: RECURRENT SMALL BOWEL MYOSARCOMA.

Acknowledgment: The editors wish to thank Drs. Robert L. Segal and Vernon A. Weinstein for permission to publish this case.



Case 297, Fig. 1A. Prone examination of the small intestine reveals "pleating" effect on the lateral contour of a proximal jejunal loop (arrows). The mucosal folds are effaced but no discrete ulcerations are identified. There is minimal angulation and some fixation of the involved loop. There is no evidence of proximal dilatation of the jejunum.

Case 297, Fig. 1B. A later film performed during the course of the same examination reveals numerous similar nodular imprints fixing the mucosa of mid-ileal loops. Again there is some fixation but no ulcerations or obstruction.

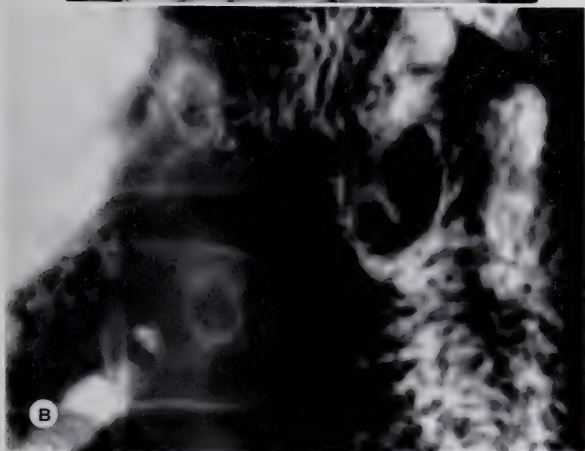


Case 297, Fig. 2. During the course of a barium enema, there is evidence of a mass adjacent to the sigmoid causing a constant contour defect without mucosal abnormalities (arrow). This is typical of a serosal implant by the tumor nodule.

CASE NO. 298

Submitted by Dr. S. G. Bluestein

A 19 year old woman was admitted to the hospital because of upper gastrointestinal bleeding. One year previously, the patient had a similar episode requiring hospitalization; the symptoms at that time were severe weakness, pallor, headache, palpitations and melena. The hemoglobin was 7 gm per cent. After blood transfusions, complete roentgen investigation of the intestinal tract revealed no abnormalities. After discharge from the hospital, periodic examinations of the stools for occult blood were positive. For several weeks prior to the present admission there was some abdominal fullness after eating, but no vomiting. A gastrointestinal series was performed which showed the presence of a constant, smooth rounded filling defect at the ligament of Treitz. This measured 2 cm at diameter and was attached with a distinct pedicle (Fig 1A, B). The lesion was believed to be benign and exploration was advised. At laparotomy, there was an oval 2 cm freely movable mass within the lumen of the proximal jejunum. It was pedunculated and no discrete ulcerations could



Case 298, Fig. 1A. There is a constant intraluminal smooth rounded polypoid filling defect within the proximal jejunum just distal to the ligament of Treitz. The involved loop is slightly dilated but there is no evidence of proximal dilatation.

Case 298, Fig. 1B. A pressure spot film of this region confirms the presence of the polypoid jejunal tumor.

be identified. Histologic diagnosis was benign adenomatous polyp. The patient made an uneventful recovery.

—*Claude Bloch*

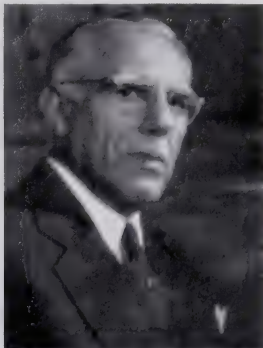
Case Report: PEDUNCULATED ADENOMATOUS POLYP AT THE LIGAMENT OF TREITZ.

Received for publication October 9, 1967.

Announcement

THE RALPH COLP AWARD FOR 1967

Dr. Claude Bloch and Dr. Harvey M. Peck are recipients of the Ralph Colp Award for 1967. The award is given for their many years of consistently high quality reporting of the "Radiological Notes" feature series that appear regularly in *The Journal of The Mount Sinai Hospital*.



This award is made by the Ralph Colp Fund, established by his colleagues and friends in honor of Dr. Ralph Colp and in recognition of his long years of distinguished service to The Mount Sinai Hospital and to American surgery.

In Memoriam

SERGEI FEITELBERG

1905-1967

Many men have contributed to the eminence of Mount Sinai and its unique clinical and scientific position through the quality of their work. Fewer encompass the group of those who, as innovators, established new academic, scientific or social enterprises which have added to the uniqueness of Mount Sinai as trailblazer in the development of American medicine. But even smaller is the circle of those who, beyond their field, influenced the intellectual climate of the institution by serving as a conscience guarding the excellence of performance, as a mouthpiece of its achievements and aspirations, and possibly most important, as a sounding board for new development and for fledgling ideas in the institution. Sergei Feitelberg is an example of those few who equally influenced the scientific growth, the pioneering in new areas and the development of the spirit of Mount Sinai. During his tenure it went from a community hospital to a research center to a medical school and shortly before his death to a key component of the City University of New York. In this frequently adverse, stormy and often confusing course, he represented a tower of strength. His crucial influence in crucial times is only superficially reflected in the cold biographical data.

Sergei Feitelberg was born in Russia in 1905. He studied at the Berlin Institute of Technology and at the University of Vienna where he was an active research worker in its famous Pharmacologic Institute under our beloved Ernst Peter Pick, a place where many members of the staff of Mount Sinai had received their scientific training. Political developments, too well known to be recalled, were responsible for his moving from Russia to Central Europe and subsequently after he had received his M.D. degree from the University of Lausanne, Switzerland in 1938, he reached this country. He came in 1939 to The Mount Sinai Hospital where his medical and physical talents found rapid recognition in the newly formed laboratory of pharmacology from which fundamental discoveries emanated. He subsequently spent two years in the Army Signal Corps during World War II. His knowledge in mathematics, biology and physics, paired with an astonishing manual skill and attention to detail, resulted in the development of various types of apparatus, then only rarely utilized in biomedical research and surely not in what was then a community hospital which was dedicated to superior medical care and to research primarily based on clinical-pathological correlation. It was this unusual combination of talents of Sergei which enabled Mount Sinai to establish the André Meyer Department of Physics in 1954 of which he became the first director and which he developed into an active research center of national and international renown. He and his co-workers became leaders in the rapidly developing field of the use of radioactive isotopes in clinical medicine. Many publications deal with biophysical and physiologic problems bespeaking these scientific activities.



SERGEI FEITELBERG, M.D.
1905-1967

Many of them have become standard publications in the field, written with the meticulous attention to language and with the clarity of expression which characterized Sergei. His books and book chapters are widely acknowledged and the Quimby-Feitelberg-Silver book is the standard text on radioactive isotopes in medicine and biology appearing in several editions and languages. The courses at Mount Sinai in this field which Sergei organized with love and compulsion are nationally and internationally famous and it is appropriate that they are now officially designated as The Dr. Sergei Feitelberg Courses on the Clinical Use of Radioactive Isotopes. Signs of national recognition were many, like membership in the National Committee on Radiation Protection, in the Human Applications Advisory Subcommittee of the Atomic Energy Commission, and in many exclusive societies as well as an Associate Clinical Professorship in Radiology at Columbia University. He resigned from this position with the development of our own medical school, to accept a professorship and the chairmanship of the Department of Biophysics of the school.

These naked data conceal more than reveal his influence upon all of us. He was, as an officer of the Medical Board and as an individual, fighting for excellence and against compromise. He took the brunt of many battles, the outcome of which was better because he fought them. He was an important factor in the development of the basic science curriculum of the medical school and in the selection of the faculty but his greatest influence is difficult to put into words and also difficult to define if one wishes to apply the clarity of thinking which characterized him and his contributions. We benefitted from our many discussions with him; often what we then expressed revealed the impact of his influence and standards.

A man of great culture, his diversified interests and indefatigable collecting made him a great friend to many people in different walks of life. Few people know as much about the mechanics of clocks, about the details of painting and music, about philosophy of science and last but not least about physics and medicine. His friends have lost much of this edifying influence which made it clear that great as Sergei was a scientist he was even greater as a man and philosopher. He was a happy person, also happy in his death, which took him in peaceful sleep, on September 15, 1967. His wife Liesl complemented his special personality to create a cultural atmosphere combining the best of this country and of the old world. With her we share the loss of a man of great achievement, influence, culture and love.

Hans Popper, M.D.
for the
Editorial Board

High Flow Whole Body Hemodilution Perfusion: Acid Base, Renal, Electrolyte and Body Fluid Alterations

MELVIN KAHN, M.D., BERNEY GOODMAN, M.D., ROBERT S.
LITWAK, M.D., AND HOWARD L. GADBOYS, M.D.

INTRODUCTION

The introduction of hemodilution in whole body perfusion has led to a considerable reduction in the number of complications previously seen with whole blood perfusion (1-15). However, the use of a dilute perfusate per se causes changes in hemodynamics, body fluid distribution, electrolyte composition and renal function which have not as yet been fully clarified (1). Moreover, published data analyzing these changes cannot be extrapolated *in toto* to apply to a different group of patients undergoing hemodilution perfusion since there is great variation in the nature of the diluent and technique of perfusion employed in different centers. The present study attempts to define the acid-base, fluid, electrolyte and renal functional alterations seen in man with three kinds of hyperosmolar perfusates. Certain conclusions applicable to hemodilution perfusion in general and also to the specific perfusates utilized in this study will be discussed.

METHODS

All patients underwent open cardiac repair for a variety of congenital and acquired lesions employing high flow hemodilution perfusion. The general methods and techniques have been previously described (1). Forty-one adult patients were studied. Prior to perfusion five percent dextrose in water, acting as a vehicle for medications, was slowly infused.

Table I outlines the composition of the perfusates employed, the volumes of the priming solutions and the volumes of perfusates added to the reservoir during perfusion. The perfusates were:

1. *DRAT I* (dextrose/Ringer's/albumin/THAM). Fifty percent ACD blood, fresh or up to five days old, and 5 percent dextrose in Ringer's solution with 1 percent albumin (Albuminsol®). In addition, 280 ml of a 0.3 molar solution (70 ml/500 ml blood) of THAM (an amine buffer-tris hydroxymethyl aminomethane) was added to the priming volume, and during perfusion this buffer was infused at a rate of 7 ml/Kg/hour

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through the venous line of the pump oxygenator. This perfusate was used in 15 patients.

2. *DRAT II*. The composition of this solution was similar to the DRAT I perfusate, except that only 140 ml of a 0.3 molar solution of THAM (35 ml/500 ml blood) was added to the priming volume and 3.5 ml/Kg/hour was infused during perfusion. This perfusate was used in 17 patients.

3. *PT (PLASMA-THAM)*. This solution consisted of 50 percent ACD blood and 50 percent homologous ACD plasma reconstituted with calcium chloride and sodium bicarbonate. 280 ml of a 0.3 molar solution of THAM was added to the priming volume but no THAM was infused during perfusion. Nine patients were studied utilizing this perfusate.

Irrespective of the perfusate employed, all procedures were performed and all specimens were collected under similar conditions in all patients.

In order to observe the alterations before, during and after perfusion, and to compare results among the three different perfusates, specimens of blood and urine were collected over similar periods from all patients. In each study period urine specimens were obtained by free flow through an indwelling Foley catheter with suprapubic pressure applied at the time of collection to completely empty the bladder. Blood specimens were drawn anaerobically into heparinized tubes through an arterial catheter pre- and postperfusion, and through the arterial perfusing line during perfusion. The designated periods of collection were:

1. *Preperfusion period*. This period extended from the induction of anesthesia until the institution of partial bypass circulation. A blood specimen was obtained within 15 minutes after induction of anesthesia and urine was collected throughout the period.

2. *Perfusion*. This period was further subdivided into: (A) early perfusion, and (B) late perfusion.

(A) *Early Perfusion*. This period of urine collection started with the inception of partial bypass circulation, and averaged 22.2, 27.2 and 34.6 minutes in DRAT I, DRAT II and PT cases respectively. A blood specimen was drawn at the end of the period.

(B) *Late Perfusion*. This period extended from the end of the early perfusion period until the end of total bypass. The periods of urine collection averaged 77.9, 100.8, and 139.8 minutes in the three groups respectively. A blood specimen was drawn at about the midpoint of the period.

3. *Postperfusion*. Urine was collected over designated periods from the end of total bypass circulation up to 42 hours postperfusion. Blood was drawn at the end of each interval. The periods were:

(A) 0 to 2 hours postperfusion.

(B) 2 to 6 hours postperfusion.

(C) 6 to 18 hours postperfusion.

(D) 18 to 42 hours postperfusion.

Biochemical measurements were made on the blood and urine collected during the study periods outlined above. The biochemical methods employed were: $p\text{CO}_2$, pH, buffer base, standard bicarbonate, and base excess were measured at 38° Centigrade by the method of Astrup (16) utilizing the nomogram of Siggard-Andersen and Engel (17). Oxygen tension was determined with a Clarke electrode adapted to the Astrup apparatus. Urine and plasma osmolalities were determined employing a Fiske osmometer. Hematocrits were determined using a micro technique. Plasma hemoglobin was determined by spectrophotometry. Plasma and urine sodium and potassium were analyzed by flame photometry using an internal lithium standard and chloride was measured potentiometrically (18). Calcium was measured by atomic absorption spectrometry (19). Glucose was analyzed by the method of Nelson (20).

Glomerular filtration rates were estimated on the basis of glucose clearance, utilizing mean glucose Tm values corrected for body surface area (21). The mid-period plasma glucose concentration was estimated by logarithmic interpolation. The following formulae were applied to make the calculations:

- (1) Filtered glucose = Excreted glucose + Reabsorbed glucose, and
 - (2) Reabsorbed glucose = TmG (when gross glycosuria is present)
 - (3) Therefore, filtered glucose = Excreted glucose + TmG
 - (4) Since filtered glucose = Plasma glucose \times GFR, then
- combining and rearranging equations (1), (2), and (3)

$$\text{GFR} = \frac{U_{\text{Glucose}}V + \text{Tm}_{\text{Glucose}}}{P_{\text{Glucose}}}$$

This technique for the calculation of glomerular filtration rate, although not reliable in any single subject because of large variation in the individual Tm for glucose, is here considered valid for the group means, since the mean Tm for glucose employed in the calculation was determined on groups of similar size to that used in this study (21).

Osmolar clearance was calculated from the formula $U_{\text{osm}}V/P_{\text{osm}}$ where U_{osm} is urine osmolality, P_{osm} is plasma osmolality and V is the rate of urine flow per minute. Free water reabsorption ($\text{T}^c\text{H}_2\text{O}$) was calculated from the formula $\text{T}^c\text{H}_2\text{O} = C_{\text{osm}} - V$.

RESULTS

Table I depicts pertinent perfusion data in the three groups. Average perfusion time was shortest in the DRAT I and longest in the PT group. In all three groups esophageal temperatures during periods of early and late perfusion were similar. Mean arterial pressures were well maintained throughout perfusion, and the levels were similar in all three groups as were mean venous pressure levels.

Table II details the mean biochemical data of the three kinds of perfusates employed. It can be seen that a higher pH was observed in the DRAT I

TABLE I
Mean Data of 41 Patients Undergoing Hemodilution Perfusion*

	DRAT I	DRAT II	PT
No. of patients	15	17	9
Patient weight (kg)	58.2(4.9)	55.9(4.5)	65.7(7.0)
Patient surface area (M ²)	1.60(0.08)	1.51(0.14)	1.73(0.09)
Total duration of perfusion (min)	100.1	128.0	174.4
Early specimen	22.2(1.6)	27.2(3.0)	34.6(6.9)
Late specimen	77.9(11.9)	100.8(12.3)	139.8(25.2)
Esophageal temperature			
Early (C°)	28.6	28.8	28.5
Late (C°)	33.0	34.0	33.1
Arterial flow rate			
(l/min)			3.75
(l/min/M ²)	3.21	3.64	2.17
Mean arterial pressure during perfusion (Brachial) (mm Hg)	2.00	2.41	67.7
Mean venous pressure during perfusion (SVC) (mm Hg)	60.9	63.6	14.5
Priming volume (ml)	18.0	14.5	4018
Blood	3250	3280	1833
DRA†	1485	1570	0
Plasma	0	0	1833
THAM‡	280	140	280
NaHCO ₃ §	0	0	43
CaCl ₂	0	0	29
Perfusate added during perfusion (ml)	3093	2822	1547
Blood	1245	1207	772
DRA	1245	1207	0
Plasma	0	0	772
THAM	603	408	0
NaHCO ₃	0	0	1
CaCl ₂	0	0	2
Total perfusate employed (ml)	6343	6102	5565
(ml/kg)	109.0	109.2	84.7
(ml/kg/hr)	65.3	51.2	29.1
Percent diluent	57	54	53

* Mean \pm (1 standard error) where indicated.

† DRA is 5% dextrose in Ringer's solution with 1% albumin.

‡ THAM is a 0.3 M solution in 5% dextrose in water.

§ NaHCO₃—44.6 mEq/50 ml

|| CaCl₂—1 gm/10 ml

and PT perfusates. This was attributable to the greater volume of THAM added to these solutions. The addition of sodium bicarbonate to the PT perfusate further contributed to the alkalinity of this perfusate and caused the actual bicarbonate level to be roughly double that of the other two solutions. The electrolyte composition of the three perfusates was similar except for the marked hypercalcemia noted in the PT solution. This was

TABLE II
Biochemical Data of the Three Perfusates Employed*

Determination†	DRAT I	DRAT II	PT.
pH (units)	7.56(0.04)	7.35(0.02)	7.59(0.02)
pCO ₂ (mm Hg)	13(0.6)	16(0.6)	24(1.7)
Actual bicarbonate (mEq/l)	11.0(0.6)	9.0(0.7)	22.0(0.8)
Base excess (mEq/l)	-10.5(1.0)	-15.9(0.7)	+2.4(0.8)
pO ₂ (mm Hg)	140(5.8)	143(12.6)	137(9.4)
Osmolality (mOsm/kg)	457(2.3)	456(2.1)	344(8.3)
Glucose (mg/100 cc)	2504(97)	2234(110)	897(175)
Sodium (mEq/l)	148(1.8)	149(1.4)	155(3.5)
Potassium (mEq/l)	6.6(0.3)	5.9(0.2)	5.8(1.1)
Chloride (mEq/l)	116(1.6)	120(1.8)	93(1.7)
Calcium (mg/100 cc)	11.2(0.3)	11.8(0.3)	26.0(1.8)
Hematocrit	17.6(0.4)	18.8(0.5)	17.0(1.3)
Plasma hemoglobin (mg/100 cc)	15.0(2.3)	20.0(2.1)	40.0(4.6)

* Mean \pm (1 standard error)—data obtained after mixing and recirculation (room air).

† Acid-base data measured and recorded at 38°C. (See methods.)

attributable to the large amount of calcium added to neutralize the citrate in the ACD blood and plasma. It should be noted that under these conditions total calcium values are not an index of the level of ionized calcium.

Hyperosmolality roughly paralleling the magnitude of the hyperglycemia was noted in all the perfusates, and was therefore least marked in the PT solution. Hematocrits and plasma hemoglobin estimations were similar in all perfusates.

Tables III, IV, and V detail the pertinent biochemical data of the arterial blood for each group.

DRAT I (Table III). Prior to perfusion all parameters measured were within normal limits. During the period of early perfusion there was a fall in pH and a rise in pCO₂ levels. There was a significant rise in plasma osmolality with a concomitant marked increase in glucose concentration. Electrolyte values remained stable. Hematocrit readings fell and reflected the dilutional effect of the dilute perfusate. Mean plasma hemoglobin rose to approximately double preperfusion levels.

There was a further fall in pH and an increase in pCO₂ noted during the late perfusion collection period. However, the degree of acidosis was not marked, and the base excess indicated "metabolic compensation" presumably due to THAM buffering. Hyperosmolality and hyperglycemia persisted but electrolyte concentrations remained stable. Hematocrit readings continued to be low and there was a further rise in plasma hemoglobin concentration. Postperfusion all parameters gradually, or rapidly, returned to preperfusion normal levels or continued to remain stable where they had been so previously. Postperfusion serum potassium levels were seen to be low in certain

TABLE III
Mean Biochemical Data (Blood) of 15 Patients Undergoing Perfusion With Perfusate DRAT I*

Determination†	Preperfusion‡	Perfusion		Postperfusion			
		Early	Late	2 hours	6 hours	18 hours	42 hours
pH	7.47 (0.02)	7.37 (0.02)	7.33 (0.01)	7.38 (0.02)	7.42 (0.01)	7.45 (0.02)	7.56 (0.04)
pCO ₂ (mm Hg)	36 (2.4)	45 (2.7)	62 (3.6)	47 (2.3)	47 (1.6)	45 (2.0)	42 (1.8)
Actual bicarbonate (mEq/l)	24.0 (0.7)	25.0 (0.7)	31.0 (1.1)	27 (0.6)	30 (0.7)	30 (0.6)	30 (1.0)
Base excess (mEq/l)	+2.1 (0.5)	+0.1 (0.5)	+4.3 (0.7)	+1.7 (0.5)	+4.8 (0.6)	+6.4 (0.5)	+6.3 (0.7)
pO ₂ (mm Hg)	242 (26)	132 (18)	171 (26)	144 (24)	123 (22)	84 (4)	75 (3)
Osmolality (mOsm/kg)	294 (1.4)	327 (3.2)	332 (2.6)	318 (2.7)	303 (2.4)	287 (2.0)	274 (2.2)
Glucose (mg/100 cc)	177	852 (34)	751 (34)	535 (43)	276 (32)	162	140
Sodium (mEq/l)	143 (1.5)	134 (1.7)	134 (1.8)	143 (1.7)	146 (1.4)	143 (0.8)	137 (2.2)
Potassium (mEq/l)	5.8 (0.2)	5.6 (0.2)	5.5 (0.3)	4.8 (0.2)	4.9 (0.3)	3.8 (0.2)	3.6 (0.1)
Chloride (mEq/l)	101 (1.0)	100 (1.5)	99 (1.3)	100 (1.3)	101 (1.6)	99 (1.2)	96 (1.4)
Calcium (mg/100 cc)	9.1 (0.2)	9.1 (0.2)	8.8 (0.2)	9.9 (0.2)	9.7 (0.1)	9.4 (0.2)	9.2 (0.3)
Hematocrit	42 (1.3)	30 (0.9)	31 (1.2)	41 (0.8)	42 (0.8)	39 (1.4)	38 (1.)
Plasma hemoglobin (mg/100 cc)	12.0 (1.1)	22.0 (3.2)	38.0 (5.2)	40.0 (4.1)	21.0 (0.8)	10.0 (0.9)	—

* Mean \pm (1 standard error).

† Acid-base data measured and recorded at 38°C. (See methods.)

‡ Preperfusion specimen obtained within 15 minutes after induction of anesthesia.

TABLE IV
Mean Biochemical Data (Blood) of 17 Patients Undergoing Perfusion With Dilute Perfusate DRAT II*

Determination†	Preperfusion‡	Perfusion		Postperfusion			
		Early	Late	2 hours	6 hours	18 hours	42 hours
pH	7.42(0.05)	7.27(0.02)	7.19(0.02)	7.32(0.02)	7.39(0.01)	7.40(0.01)	—
pCO ₂ (mm Hg)	38(1.9)	46(2.8)	72(4.1)	44(2.1)	46(2.0)	45(1.6)	—
Actual bicarbonate (mEq/l)	24.0(0.7)	20.0(0.7)	26.0(1.1)	22.0(0.9)	26.0(1.1)	27.0(0.8)	—
Base excess (mEq/l)	-1.5(0.8)	-5.4(0.7)	-2.6(0.9)	-3.4(0.9)	+1.3(0.2)	+2.7(0.2)	—
pO ₂ (mm Hg)	211(18)	109(16)	177(26)	182(24)	115(15)	90(5)	—
Osmolality (mOsm/kg)	290(1.2)	322(1.6)	329(3.1)	317(2.4)	307(2.9)	290(2.0)	279(2.3)
Glucose (mg/100 cc)	168	825(59)	728(45)	458(31)	220(22)	148	125
Sodium (mEq/l)	141(1.6)	136(1.8)	136(1.5)	144(1.8)	143(1.8)	140(2.0)	140(1.8)
Potassium (mEq/l)	5.0(0.3)	4.7(0.3)	5.0(0.3)	4.7(0.3)	4.4(0.2)	3.8(0.2)	4.3(0.3)
Chloride (mEq/l)	103(1.1)	103(1.2)	102(1.1)	104(1.1)	105(1.3)	103(1.2)	98(2.0)
Calcium (mg/100 cc)	9.0(0.1)	8.5(0.3)	9.0(0.1)	9.7(0.2)	9.3(0.2)	8.9(0.1)	8.6(0.2)
Hematocrit	42(1.4)	32(0.9)	34(1.1)	41(0.7)	41(0.8)	39(1.3)	—
Plasma hemoglobin (mg/100 cc)	17.0(4.3)	31.0(4.0)	57.0(4.3)	50.0(4.4)	27.0(2.2)	14.0(0.9)	—

* Mean \pm (1 standard error).

† Acid-base data measured and recorded at 38°C. (See methods.)

‡ Preperfusion specimen obtained within 15 minutes after induction of anesthesia.

TABLE V
Mean Biochemical Data (Blood) of 9 Patients Undergoing Perfusion With Dilute Perfusate PT*

Determination†	Preperfusion†	Perfusion		Postperfusion			
		Early	Late	2 hours	6 hours	18 hours	42 hours
pH	7.44 (0.03)	7.32 (0.02)	7.19 (0.03)	7.37 (0.03)	7.40 (0.02)	7.44 (0.02)	7.47 (0.02)
pCO ₂ (mm Hg)	39 (3.7)	59 (4.7)	95 (8.1)	49 (6.7)	46 (2.3)	43 (1.7)	42 (1.9)
Actual bicarbonate (mEq/l)	25.0 (1.0)	29.0 (1.6)	35.0 (1.2)	26.0 (1.8)	28.0 (1.0)	28.0 (0.9)	29.0 (0.6)
Base excess (mEq/l)	+1.1 (0.9)	+1.7 (0.2)	+0.7 (1.5)	+0.6 (1.3)	+2.7 (0.9)	+4.3 (0.9)	+6.0 (0.6)
pO ₂ (mm Hg)	215 (41)	107 (17)	190 (34)	122 (14)	195 (45)	105 (19)	107 (25)
Osmolality (mOsm/kg)	288 (2.5)	298 (1.6)	307 (3.4)	307 (3.3)	292 (2.6)	283 (1.8)	271 (2.2)
Glucose (mg/100 cc)	182	314 (34)	353 (38)	326 (41)	286 (40)	153	144
Sodium (mEq/l)	137 (2.1)	140 (2.3)	139 (1.8)	140 (2.0)	141 (1.8)	139 (2.0)	136 (2.2)
Potassium (mEq/l)	4.7 (0.3)	4.6 (0.3)	4.5 (0.3)	4.4 (0.2)	4.6 (0.2)	4.1 (0.2)	4.8 (0.5)
Chloride (mEq/l)	100 (2.9)	96 (1.8)	94 (2.3)	98 (0.9)	95 (1.9)	95 (1.7)	97 (2.4)
Calcium (mg/100 cc)	9.3 (0.2)	14.3 (0.6)	12.2 (0.4)	11.0 (0.4)	10.5 (0.3)	9.5 (0.3)	9.1 (0.3)
Hematoerit	41 (0.8)	31 (0.7)	33 (0.9)	36 (1.0)	35 (1.7)	34 (1.8)	31 (2.0)
Plasma hemoglobin (mg/100 cc)	15.0 (1.6)	34.0 (4.1)	64.0 (5.7)	51.0 (6.5)	30.0 (4.5)	15.0 (1.4)	—

* Mean \pm standard error.

† Acid-base data measured and recorded at 38°C. (See methods.)

‡ Preperfusion specimen obtained within 15 minutes after induction of anesthesia.

TABLE VI
Mean Biochemical Data* of the Urine of 15 Patients Undergoing Perfusion with Dilute Perfusate DRAT I

Determination	Preperfusion	Perfusion		Postperfusion			
		Early	Late	0-2 hrs.	2-6 hrs.	6-18 hrs.	18-42 hrs.
Volume (ml/min)	0.55(0.12)	2.43(0.42)	6.38(1.25)	6.24(0.57)	2.06(0.28)	0.67(0.07)	0.80(0.12)
Glomerular filtration rate (ml/min)	—	95.0(5.0)	55.0(4.0)	70.0(5.0)	95.0(11.0)	—	—
Urine osmolality (mOsm/kg)	573(29.9)	468(29.3)	382(13.7)	396(8.5)	524(30.7)	731(33.0)	453(62.6)
Total solute (μ Osm/min)	315(57)	1137(202)	2435(410)	2471(196)	1080(125)	490(56)	362(59)
U _{Na} V (μ Eq/min)	30(10)	58(14)	152(51)	101(15)	45(10)	35(9)	27(6)
U _K V (μ Eq/min)	48(9)	144(32)	132(24)	148(21)	81(16)	53(8)	37(6)
U _{Cl} V (μ Eq/min)	48(15)	155(30)	451(87)	521(47)	211(33)	64(8)	33(7)
U _{Glu} V (μ M/min)	—	390(73)	983(152)	957(85)	252(37)	18	6
T ^e H ₂ O (ml/min)	0.63(0.12)	1.10(0.26)	0.97(0.22)	1.55(0.15)	1.52(0.19)	0.97(0.13)	0.55(0.15)
Cosm (ml/min)	1.08(0.20)	3.46(0.62)	7.73(1.26)	7.78(0.61)	3.57(0.41)	1.71(0.19)	1.30(0.23)

* Mean \pm (1 standard error).

patients. In addition, there was a variable but small fall in chloride concentration in a number of patients.

DRAT II (Table IV). The changes and the trend of changes noted in this group were very similar to those observed in the DRAT I group. However, compared to the DRAT I group, the fall in pH during the periods of early and late perfusion was more marked, and the $p\text{CO}_2$ levels were significantly higher during late perfusion. A small base deficit was apparent. Postperfusion recovery was rapid and normohydric conditions soon obtained.

PT (Table V). Observations made on patients in this group again showed alterations similar to those observed in the other two groups with a similar trend towards the reattainment of normal values early in the postperfusion period. In this group the acidosis noted was similar to that seen in the DRAT II group, but the $p\text{CO}_2$ levels were considerably higher in late perfusion. Very little variation in the base excess was noted.

Noteworthy in the PT group were the high serum calcium levels in early and late perfusion consequent to the large amount of calcium chloride added to the plasma component of this perfusate.

Tables VI, VII, and VIII detail pertinent urine biochemical data for each group.

DRAT I. (Table VI). During the period from induction of anesthesia to the initiation of extracorporeal circulation (preperfusion), the rate of urine flow was low and reflected the marked antidiuretic effects of the preoperative fast, anesthesia, the presence of congestive heart failure in some patients and the fall in glomerular filtration rate known to occur during anesthesia and thoracotomy. There were marked individual variations in urine osmolality, total solute and electrolyte excretion, indicated by the large standard errors of the mean values. These differences resulted from the large variations in preoperative sodium intake, the presence or absence of congestive heart failure and/or previous diuretic therapy. The effect of these factors was further reflected by the high urinary potassium to sodium ratio in many of the patients.

There was a significant and early increase in urinary flow rate during perfusion with the minute volume reaching the highest levels during late perfusion. This increase persisted during the period 0 to 2 hours postperfusion and to a lesser degree up to 6 hours postperfusion. Associated with this increase in the urine flow rate there was up to a seven-fold rise in solute excretion which persisted for a similar period of time. However, despite the observed increase in urine and solute excretion there was a significant fall in glomerular filtration rate which was best appreciated in the period of late perfusion. Recovery of the glomerular filtration rate was apparently completed 2 to 6 hours postperfusion. Figure 1 depicts the relationship between urine flow rate, solute excretion and glomerular filtration rate.

The excretion of electrolytes in the urine was modestly elevated during perfusion and for at least two hours postperfusion. The marked increase

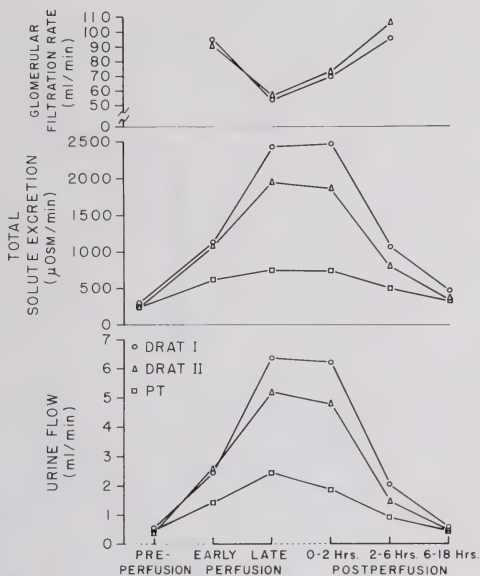
RELATIONSHIP BETWEEN GFR, URINE FLOW, AND
TOTAL SOLUTE EXCRETION

Fig. 1. Mean urine flow, solute excretion and glomerular filtration rate during each period of urine and blood collection for all three perfusates.

in chloride excretion was seen to be out of proportion to the modest increase in sodium and potassium excretion. This reflected the excretion of cationic THAM (Fig 2). Glucose excretion rose markedly and the glycosuria persisted up to six hours postperfusion.

During perfusion there was a fall in urine osmolality most marked in late perfusion. Furthermore, despite an increase in solute clearance, the rate of free water reabsorption remained considerably depressed. This depression of $\text{T}^2\text{H}_2\text{O}$ generation could not be completely attributed to the fall in glomerular filtration rate since, as can be seen in Figure 3, adjusting all values to a standard GFR of 100 ml per minute still showed a markedly defective concentrating capacity when compared to normal subjects.

DRAT II (Table VII). The changes observed in this group of patients were similar to those seen with the previous group. However, the rate of urine flow, total solute excretion, electrolyte excretion and glucose excretion

CALCULATED EXCRETION OF CATIONIC THAM

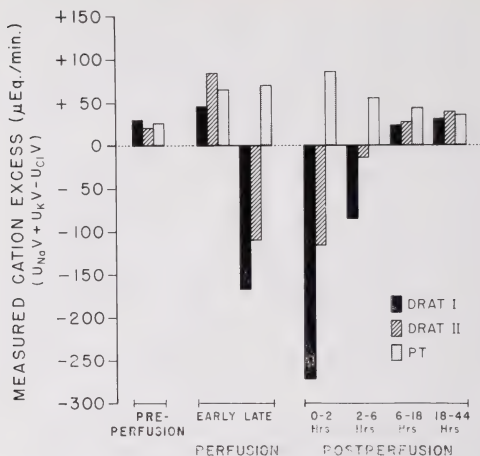


Fig. 2. The difference between the sum of the major cations and the chloride excretion rates is indicated for each study period for all perfusates. The excess of chloride excretion above that of sodium and potassium during and immediately postperfusion is an estimation of the rate of excretion of cationic THAM.

were of somewhat lesser magnitude than noted with the DRAT I group. Again, however, the glomerular filtration rate was seen to be markedly depressed in late perfusion (Fig 1), and the rate of $\text{T}^{\text{c}}\text{H}_2\text{O}$ generation was reduced. The defective concentrating capacity was not correctable to normal ranges by compensating for the fall in the glomerular filtration rate (Fig 3).

PT (Table VIII). The trend of changes observed in this group, perfused with the PT solution, was similar to that noted with the other two perfusates. However, the magnitude of the changes was considerably less and urinary flow rate, total solute, electrolyte and glucose excretion were only moderately enhanced during perfusion and up to six hours postperfusion. It is also noteworthy, that in this group, in marked contrast to the other two groups, urinary chloride excretion was not significantly greater than the excretion of sodium and potassium (Fig 2).

DISCUSSION

Although much of the evidence favoring the use of dilute perfusate had been obtained from studies in animals and inferred from *in vitro* studies

$T_{H_2O}^C - C_{OSM}$ RELATIONSHIP IN
41 PATIENTS UNDERGOING HEMODILUTION PERFUSION

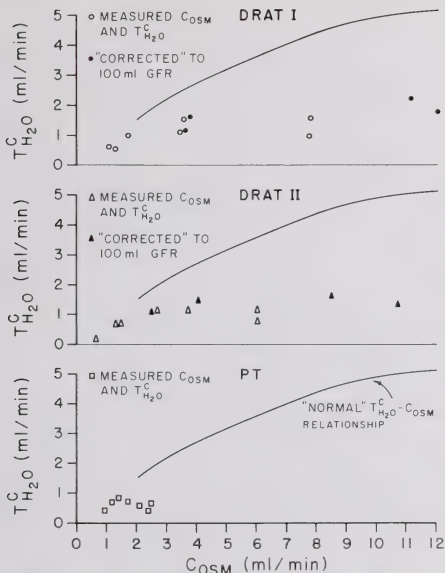


FIG. 3. The mean $T_{H_2O}^C - C_{OSM}$ relationships for all periods with the three different perfusates. In the DRAT I and DRAT II groups the points at C_{OSM} greater than 3 ml/min represent the perfusion and immediate postperfusion periods. Curves corrected for a glomerular filtration rate of 100 ml/min are depicted for the DRAT I and DRAT II groups. The "normal" $T_{H_2O}^C - C_{OSM}$ relationship (42) is superimposed in each diagram.

(2-10, 22, 23), it is probable that these observations are pertinent to the clinical use of these perfusates in man. It is now well established that the use of hemodilution perfusate has considerably lessened the incidence of postperfusion complications (1, 11-15).

In the present study 41 patients have undergone total cardiopulmonary bypass in a high flow large prime system. In two groups of patients, two crystalloidal electrolyte solutions, differing only in the amount of buffer added, were used as diluents and in a third group plasma was used as the diluent. Hypothermia was employed in all patients. Although alterations in acid-base balance, body fluid and electrolyte composition, and renal function were noted with all the perfusates, the qualitative changes were

TABLE VII
Mean Biochemical Data of the Urine of 17 Patients Undergoing Perfusion with Dilute Perfusate DRAT II*

Determination	Preperfusion	Perfusion		Postperfusion			
		Early	Late	0-2 hrs.	2-6 hrs.	6-18 hrs.	18-42 hrs.
Volume (ml/min)	0.42 (0.13)	2.59 (0.72)	5.24 (0.69)	4.83 (0.49)	1.47 (0.21)	0.65 (0.09)	0.82 (0.10)
Glomerular filtration rate (ml/min)	—	92.0 (8.0)	56.0 (6.0)	71.0 (6.0)	106.0 (11.0)	—	—
Urine osmolality (mOsm/kg)	543 (41.6)	463 (36.7)	375 (16.8)	392 (8.3)	550 (18.3)	583 (76.9)	457 (60.6)
Total solute (μ Osm/min)	228 (25)	1199 (134)	1964 (228)	1893 (179)	809 (109)	379 (34)	375 (36)
U _{Na} V (μ Eq/min)	13 (3)	90 (28)	180 (39)	117 (33)	32 (7)	27 (7)	27 (6)
U _K V (μ Eq/min)	25 (3)	140 (28)	83 (14)	105 (17)	56 (11)	42 (7)	38 (5)
U _{Cr} V (μ Eq/min)	18 (4)	147 (29)	373 (55)	339 (50)	101 (14)	42 (5)	26 (4)
U _{Glucose} V (μ M/min)	—	329 (65)	681 (32)	646 (74)	189 (49)	19	5
T-H ₂ O (ml/min)	0.18 (0.11)	1.13 (0.22)	0.74 (0.18)	1.16 (0.15)	1.12 (0.15)	0.66 (0.11)	0.72 (0.11)
Cosm (ml/min)	0.61 (0.10)	3.70 (0.42)	5.98 (0.70)	6.00 (0.58)	2.65 (0.35)	1.32 (0.12)	1.48 (0.14)

* Mean \pm (1 standard error).

similar. Differences in the results obtained with the three groups of patients were, in most instances, directly attributable to the differences in the composition of the perfusates employed.

Acid-Base Balance

The acidosis frequently observed during total cardiopulmonary bypass is believed to result from inadequate tissue perfusion with resultant anoxia and the production of excess amounts of lactic acid (24, 25). The acidosis may be further aggravated by the use of hypothermia. During hypothermia increased solubility of carbon dioxide and an increased affinity of hemoglobin for oxygen impairs the release of oxygen from tissues and potentiates anaerobic metabolism (26). Cardiovascular and or renal complications may result from this acidosis (27, 28). The severity of the acidosis may be lessened by the use of high flow, large prime system which may provide more adequate peripheral perfusion (25).

Although sodium bicarbonate is the usual buffer utilized to correct metabolic acidosis, an amine buffer, such as THAM, offers certain advantages under conditions of whole body perfusion. Sodium bicarbonate is primarily an extracellular buffer and increases the sodium load. THAM permeates cell membranes freely and therefore presumably exerts its buffering action at a more extensive and physiologic site (29) and, because of its intracellular distribution (30) and its behavior as a solute diuretic in the renal tubules (31) is less likely than sodium bicarbonate to increase the intravascular volume.

The present data suggest that the metabolic acidosis, although increasing during perfusion in our patients, was inversely related to the amount of THAM employed, being greatest in the group with the least buffer. An overcompensation of the metabolic acidosis was seen in early perfusion, before excess lactate had accumulated, when large amounts of THAM were used. In addition to these metabolic alterations of acid-base balance, there was an increase in arterial $p\text{CO}_2$ levels noted in the three groups. Inadequate mixing of gases in the Gibbon-Mayo oxygenator was implicated in the hypercapnia during these studies. This mechanical defect has been subsequently corrected and $p\text{CO}_2$ levels at end-perfusion have been normal.

However, since acid-base parameters change markedly with temperature (32-34), an accurate interpretation of any patient's acid-base status is dependent on pertinent measurements being made *at the temperature of the patient* (26). During perfusion patients included in this study were hypothermic although measurements of pH and $p\text{CO}_2$ were made on the Astrup apparatus after the blood was warmed to 38° Centigrade. Warming a solution of electrolytes increases ionization and will, therefore, increase hydrogen ion concentration. Hence, the same solution at 38° Centigrade is more acid than at 28° Centigrade. Within the range of temperature utilized in this study, the pH of whole blood has been shown to increase 0.0147 units per degree fall in temperature (33). Nomograms have been developed

TABLE VIII
Mean Biochemical Data of the Urine of 9 Patients Undergoing Perfusion with Dilute Perfusate PT*

Determination	Preperfusion	Perfusion		Postperfusion			
		Early	Late	0-2 hrs.		6-18 hrs.	
				2-6 hrs.		18-42 hrs.	
Volume (ml/min)	0.50(0.13)	1.43(0.47)	2.48(0.73)	1.79(0.20)	0.97(0.29)	0.53(0.10)	0.54(0.9)
Urine osmolality (mOsm/kg)	542(49.1)	428(40.1)	305(7.3)	435(30.6)	532(43.0)	738(65.6)	622(92.2)
Total solute (μ Osm/min)	271(70)	612(137)	756(201)	779(90)	516(115)	391(95)	336(60)
U _{Na} V (μ Eq/min)	39(23)	57(27)	112(52)	45(11)	36(12)	18(8)	10(6)
U _K V (μ Eq/min)	34(6)	84(15)	77(15)	99(20)	49(12)	45(12)	39(8)
U _{Cl} V (μ Eq/min)	47(27)	76(11)	119(56)	58(15)	31(7)	20(5)	13(2)
U _{Glucose} V (μ M/min)	—	80(36)	69(14)	111(24)	44(12)	11	6
T ¹⁸ H ₂ O (ml/min)	0.45(0.15)	0.62(0.08)	0.44(0.16)	0.69(0.19)	0.76(0.15)	0.83(0.23)	0.71(0.20)
Cosm (ml/min)	0.95(0.25)	2.10(0.47)	2.40(0.67)	2.50(0.31)	1.70(0.28)	1.40(0.33)	1.20(0.24)

* Mean \pm (1 standard error).

TABLE IX

Mean Acid-Base Data During Perfusion in 41 Patients Uncorrected
and Corrected for Hypothermic Temperatures†*

Measurement	DRAT I		DRAT II		PT	
	Early Perfusion	Late Perfusion	Early Perfusion	Late Perfusion	Early Perfusion	Late Perfusion
Esophageal temperature (C°)	28.6	33.0	28.8	34.0	28.5	33.1
pH (units)						
Uncorrected	7.37	7.33	7.27	7.19	7.32	7.19
Corrected	7.51	7.40	7.41	7.25	7.46	7.26
pCO ₂ (mm Hg)						
Uncorrected	45	62	46	72	59	95
Corrected	28	48	30	60	38	75
Standard bicarbonate (mEq/l)						
Uncorrected	25.0	31.0	20.0	26.0	29.0	35.0
Corrected	28.0	28.5	18.4	25.4	26.5	32.1

* Measured at 38°C.

† Corrected by nomogram to temperature of patient (see text).

(35) to estimate the pH, pCO₂ and actual bicarbonate concentrations of the blood for any *in vivo* temperature when *in vitro* measurements have been made at 38° Centigrade, as in this study. The results of such a correction are depicted in Table IX. It can be seen by comparing the mean uncorrected values (measured at 38° Centigrade) and the mean corrected values (by nomogram to temperature of patient) in the DRAT I group, that the apparent mild acidosis and pCO₂ elevation in early perfusion is in fact an *in vivo* respiratory alkalosis in hypothermic subjects. In late perfusion the corrected values indicate a normal pH and only slightly elevated pCO₂ levels, whereas when measured at 38° Centigrade, an appreciable hypercapnia was indicated. Similar modifications of pH and pCO₂ levels were noted in early and late perfusion in the other two groups after correction (Table IX), but in these (DRAT II and PT), a moderate degree of respiratory acidosis was still seen to be present in late perfusion and pCO₂ levels remained significantly elevated even when corrected for temperature.

The corrections for temperature from the nomogram only approximate the actual measured values observed when determinations are performed with the Astrup set at the patient's hypothermic body temperature. The inaccuracies of the nomogram with hemodilution perfusion result from variations in hematocrits and buffer systems in such perfusions since the nomogram was devised from measurements made on whole blood (36).

Although it appears on superficial examination that the relatively normal pH values seen throughout perfusion in the DRAT I group when measured at 38° Centigrade indicate an ideal perfusate with regard to acid-base regulation, the correction for temperature unmasks a rather extreme degree of *in vivo* alkalosis in early perfusion and isohydric conditions during late

perfusion. This alkalosis might be of etiologic importance in the incidence of ventricular arrhythmias, since the incidence of this complication is reduced by maintaining an acid pH (37). Indeed, Edmark (37) has suggested that an absolute acidosis, i.e. actual pH less than 7.40 in the patient, be maintained in the patient during hypothermic perfusion. Therefore, the acid-base data obtained in the DRAT I patients, although normal when measured at 38° Centigrade, indicates *in vivo* alkalosis and suggests overbuffering with THAM. A better approximation of ideal *in vivo* balance is found in the DRAT II and PT patients and, in all perfusions after this study, we have utilized the THAM buffer in amounts used in our DRAT II subjects (140 ml 0.3 M THAM in the priming volume and 3.5 ml/Kg/hour infused throughout perfusion).

Renal Function

Prior to the institution of cardiopulmonary bypass, urine flow rates were low, a consequence of the preoperative dehydration, the frequent presence of congestive heart failure, anesthesia, and thoracotomy. Total solute excretion was also low and consisted solely of electrolyte and urea. With the onset of perfusion and for up to six hours thereafter large amounts of glucose and THAM appeared in the urine, with enhanced urine flow rates and electrolyte excretion. Six hours postperfusion there was a return to near preoperative rates of urine flow and solute excretion. This is shown diagrammatically for each period of collection in all three groups in Figure 4.

The solute diuresis noted with perfusion was particularly large in the DRAT I and DRAT II groups and is related to the marked glucose and THAM loads in these groups. Since about 80 percent of the THAM excreted in the urine at a neutral pH is in the cationic form, the excretion of chloride ions is obligated (38). The increased rate of chloride excretion which is out of proportion to the increased excretion of sodium and potassium, during and immediately following perfusion, reflects this, as can be seen in Figure 2, where "cation balance" is calculated as $UNaV + UKV - UCLV$. This large obligatory loss of chloride frequently resulted in a postoperative mild hypochloremia and was sometimes of importance in determining appropriate postoperative fluid and electrolyte administration.

Although the evidence is fragmentary at present, it is possible that the solute diuresis which accompanies the use of hyperosmolar perfusates is instrumental in preventing postperfusion acute tubular necrosis and renal failure (39, 40). However, the diuresis associated with hemodilution perfusion must not be construed as indicating normal renal function. It can be readily appreciated from the measurements of GFR, urine osmolality and T^2H_2O generation in this study that renal function is, in fact, markedly impaired during perfusion despite the presence of a marked increase in the rate of urine flow. The relationship between the urinary flow rates, solute excretion and the GFR is depicted in Figure 1. The enhanced urine excretion is a

URINE SOLUTE EXCRETION

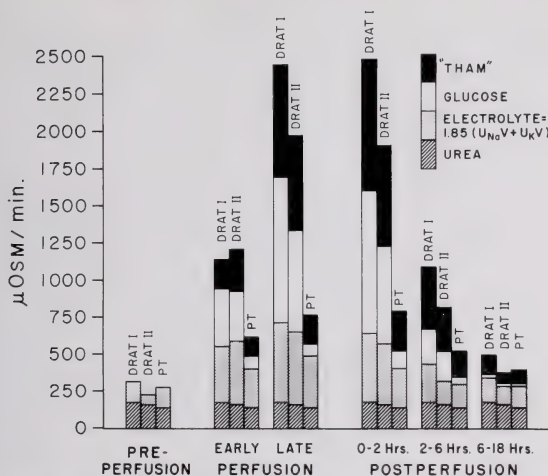


Fig. 4. Calculated mean urinary THAM, glucose, electrolyte and urea excretion in each study period with the three perfusates employed. THAM excretion has been calculated as the difference between total solute excretion and the sum of glucose, urea and electrolyte excretions.

consequence of the load of THAM and glucose acting as osmotic "non-reabsorbable" solutes. The diuresis therefore occurs in spite of a reduction of GFR to about one-half of the postoperative level.

The depression of GFR appears to be a result of cardiopulmonary bypass *per se*, and is not solely a consequence of the effects of anesthesia and/or thoracotomy. Indeed, GFR increased significantly ($p < 0.001$) in the two hours following perfusion, when the patients were still anesthetized. Similar observations have been made with the DRAT I perfusates in dogs (41).

That a diminished capacity of the kidney to concentrate the urine and generate $\text{T}^{\text{c}}\text{H}_2\text{O}$ is present during perfusion is evident from Figure 3. That the fall in GFR is not the sole determinant of this impairment is also apparent. In this figure $\text{T}^{\text{c}}\text{H}_2\text{O}$ and Cosm have been calculated per 100 ml of GFR and the mean values for each period of each group indicated. A curve relating $\text{T}^{\text{c}}\text{H}_2\text{O}$ to Cosm in normal subjects is shown for comparison (42). The marked disparity between the "normal" curve and the "corrected" values obtained in our subjects during and immediately postperfusion suggests that factors other than the depression in GFR are etiologic in the impairment of renal concentrating capacity.

Alterations in tubular absorption of sodium in the ascending limb of the loop of Henle or in medullary blood flow are of prime importance in changing the concentration of the medullary interstitium and hence the formation of hyperosmolar urine and the generation of $\text{T}^c\text{H}_2\text{O}$ (43). One or both of these may be adversely affected by perfusion. Although enhanced medullary blood flow may occur by shunting of intrarenal blood with consequent wash-out of medullary solute this has not been determined during perfusion. On the other hand, we have previously reported (44) that the normal elaboration of $\text{T}^c\text{H}_2\text{O}$ during a solute diuresis is dependent on the adequate delivery of sodium to the ascending limb of the loop of Henle prior to the initiation of the diuresis. It may therefore be surmised that prior to, or at the onset of cardiopulmonary bypass, when blood pressure is unstable and glomerular filtration absent or intermittent, solute delivery to the ascending limb is impaired. This might result in depletion of the medullary interstitium and impairment of $\text{T}^c\text{H}_2\text{O}$ generation when the solute diuresis subsequently ensues.

It should be noted that such a defect in $\text{T}^c\text{H}_2\text{O}$ during and immediately following perfusion does not necessarily indicate intrinsic renal damage. Conversely, a diminished urine concentration observed postoperatively, *at low rates of urine flow and solute clearance*, might be suggestive of either intrinsic renal damage or a marked hypodynamic state such as occurs in shock.

Body Fluid Distribution

The rapid introduction of large volumes of relatively nonphysiologic perfusate into the circulation is associated with marked dynamic fluid shifts between the intra- and extracellular compartments (45). These fluid movements tend to result postoperatively in a contraction of the intravascular volume, a contraction of intracellular volume (with potentiation of hypokalemia as this is repleted) and possibly an initial increase in interstitial volume which may be dissipated by the persistent solute diuresis. These changes would explain the frequent requirement of these cardiac patients for blood and or saline infusions with potassium supplements postoperatively in order to maintain hemodynamic stability. It must be emphasized that this postoperative fluid requirement may not be necessary when other perfusates are employed.

It is evident that the rapid introduction into the circulation of a large volume of a relatively non-physiologic solution must in itself be associated with changes of acid-base balance, body fluid and electrolyte composition and renal function. These changes would in part be dependent upon the specific composition of the perfusate employed. Consequently, comparison and interpretation of published data on the physiologic alterations observed during hemodilution perfusion must take cognizance of the specific biochemical make-up of the perfusate, the volumes of dilute perfusate used and the technical conduct of the perfusion itself.

SUMMARY

1. During extracorporeal circulation the introduction into the circulation of large volumes of hemodilute perfusate is associated with changes in acid-base balance, renal function and body fluid and electrolyte composition.
2. These changes were measured in three groups of patients each perfused with a different hemodilute perfusate (50% dilution). The amine buffer, THAM, was added to each of the three perfusates in three differing amounts.
3. The changes observed were related to the specific composition of the perfusate employed. Consequently, published data analyzing these changes cannot be extrapolated *in toto* to apply to different groups of patients undergoing hemodilution perfusion because of the great variation in the nature of the diluent employed at different centers.
4. The degree of metabolic acidosis observed during perfusion was inversely related to the amount of the buffer THAM added to the perfusate.
5. The relationship between body temperature and acid-base balance was evaluated and is discussed.
6. Plasma electrolytes were usually normal during and after perfusion. In some patients either hypokalemia and/or hyponatremia was noted postperfusion. These electrolyte aberrations may require replacement therapy.
7. A marked increase in urine flow rate was noted during and immediately after perfusion, attributable to a solute load of glucose and THAM. This occurred in spite of a reduction in glomerular filtration rate of approximately 50% during perfusion. Postperfusion, the glomerular filtration rate rapidly returned to normal.
8. A defect in the rate of $\text{T}^*\text{H}_2\text{O}$ generation during and immediately postperfusion was noted. This indicated functional derangement of the renal concentrating mechanism and was not associated with apparent renal damage.
9. Perfusion with a hypertonic hemodilution perfusate produces alterations in "compartmental" fluid distribution.

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Diabetic Neuropathy of the Upper Extremities

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Diabetic neuropathy is universally equated with symptoms and signs in the lower extremities and is rarely thought of as involving the upper extremities. Because of the clinical implications of this entity, its relative frequency, and the paucity of information in the literature, this report is presented.

REVIEW OF LITERATURE

There is scant reference to involvement of the upper extremity by diabetic neuropathy in the literature, and the few allusions are often oblique and incidental to other observations.

Symms, in 1917, observed that in those patients with diabetic peripheral neuritis who also had pain in the arms, there was an accompanying diminution of vibratory sensation in the radius and ulna (1). Bonkalo (2), in describing 74 patients with diabetic neuritis, stated that approximately one-third had absent reflexes in the upper extremities and that paresthesias were only slightly greater in the lower than the upper extremity; two of his patients had interosseous atrophy. Impairment of vibratory sensation in diabetes, especially in the index finger, has been reported in two studies (3, 4). In both, a significant increase in perception threshold was recorded as well as a lack of correlation with duration or severity of the disease, thus indicating that this phenomenon is a concomitant, rather than a complication. Collins et al., using a highly sensitive instrument, noted that 90% of diabetics had vibratory impairment in the upper extremity as compared with 98% in the lower extremity (5).

A definitive description of muscle wasting in the upper extremities of diabetics as a neuropathic phenomenon was recorded by Bischoff who described deltoid muscle atrophy (6). Seller and Szyrnski (7) reported the syndrome of "amyotrophy" as proposed in our classification; their findings in 12 cases agree with our observations with respect to objective signs, symmetry, male predominance, and the need to suspect diabetes in the presence of this finding. Pirart (8) in a review of diabetic neuropathy, recognized involvement of the upper extremities. His cases included atrophy, painless burns, and trophic lesions secondary to noxious influences; here, too, males were more commonly affected.

In a study of motor nerve conduction as measured by electromyography, Lawrence and Locke (9) noted a significant reduction in the ulnar, median and peroneal nerves in diabetics. They found that the nerves in the upper limbs are affected to the same extent as those in the lower.

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CLINICAL MANIFESTATIONS

Of the diabetic patients having neurogenic abnormalities occurring in the upper extremities, we have selected for this presentation only those with unequivocal, recognizable and definitive syndromes. This report includes thirty-five such patients, collected over the past five years.

In many of the cases, more than one expression of diabetic neuropathy was present. However, they are listed under specific headings to emphasize the salient features of each:

1. Amyotrophy
2. Asthenia
3. Sensory Impairment
4. Radiculitis

AMYOTROPHY (muscle atrophy secondary to neuropathy). The muscle atrophy is most conspicuous in the first interosseous space (Fig. 1), although it characteristically involves all the interosseous muscles of the hands bilaterally. The small muscle involvement also extends to the thenar and hypothenar eminences (Fig. 2), may include the muscles of the forearm, and is bilaterally symmetrical (Fig. 3). This manifestation of diabetic neuropathy is so clinically apparent and typical, that when one sees symmetrical bilateral



FIG. 1. Interosseous atrophy, most evident in the first interosseous space.



FIG. 2. Atrophy of thenar and hypothenar eminences.

interosseous atrophy of the hands not readily explained by any other neurological entity, the diagnosis of diabetes must be suspected and the necessary steps taken to confirm or eliminate this diagnosis. It is the most readily recognizable representation of diabetic neuropathy of the upper extremities, and was present in 24 of our 35 cases.

The following case report illustrates the fact that bilateral symmetrical interosseous atrophy of the hand muscles may be the presenting initial clinical manifestation of the disease leading to the diagnosis of diabetes (19):

Case I. A 72 year old man was admitted to the medical service for investigation of splenomegaly which led to the diagnosis of myeloid metaplasia. There was neither history nor symptoms of diabetes. One year prior to admission he had noted pains in the legs on walking, and six months previously, ulcerations developed over the lateral malleoli. The admission symptom was severe gingival bleeding which required suturing. On examination the liver and spleen were greatly enlarged and palpable. No pulses were palpable below the popliteal arteries, and there were bilateral purulent malleolar ulcerations. Neurological examination was normal except for absent ankle jerks and very advanced bilateral symmetrical atrophy involving the interosseous muscles of the hands, and the thenar and hypothenar eminences. The fasting blood sugar was 88 mg/100 cc and routine urinalysis was negative. Nevertheless, because of the highly characteristic abnormalities in the hands, a glucose tolerance



FIG. 3. Bilateral symmetry of the amyotrophy.

test was done which was diagnostic of diabetes and accompanied by glycosuria at two hours. An electromyogram was abnormal, confirming the presence of nerve pathology. Blood Wassermann was negative. X-ray films of the cervical-lumbar-sacral spine and myelogram were normal. Lumbar puncture was normal except for a spinal fluid protein of 64 mg/100 cc.

The recognition of the hand small muscle atrophy was the clue that led to the diagnosis of diabetes in this instance.

The atrophy is usually, though not necessarily, restricted to the hands. Indeed, in some instances, the deltoids, biceps, triceps and shoulder girdle muscles may be as intensely atrophied as the hand muscles. The following case report documents such involvement of the proximal portion of the upper extremities on a diabetic basis:

Case II. A 63 year old man had diabetes for 20 years. His chief complaint was progressive inability to perform all muscular movements including walking because of weakness and pain of one year's duration. One year previously his diabetes was found to be very poorly controlled. Treatment was started with oral hypoglycemic agents (tolbutamide) and three weeks later his leg difficulties began. The tolbutamide was continued for three months but because of inadequate control, he was shifted to insulin, and was now receiving 35 units NPH insulin every morning.

Three months before admission there was increased severity of aching and



Fig. 4. Bilateral symmetrical atrophy of proximal muscles and shoulder girdle.

pain as well as weakness, loss of muscle power and unsteadiness of gait. In addition, he had noticed progressive mental depression accompanied by crying spells. System review included progressive constipation for the previous year and nocturia three or four times for the previous few months. In the previous year he had lost 20 pounds.

Examination disclosed a liver palpable three fingerbreadths below the costal margin. The ocular fundi contained a few small hemorrhages bilaterally. Blood pressure 142/82 mm Hg. The posterior tibial and dorsalis pedis pulses were diminished. Rectal examination demonstrated a very relaxed sphincter.

There was marked wasting of all muscles throughout the body, most noticeable in the upper extremities and shoulder girdle (Fig 4). No fasciculations were noted. The knee jerk, ankle jerk, biceps, and triceps reflexes were absent. Vibratory sensation was impaired below the iliac crests; position sense was impaired in the toes but was preserved in the fingers; generalized muscle tenderness on deep pressure was elicited.

Intensive investigations, including liver function tests, radioactive I^{131} uptake, Schilling test, intravenous pyelogram, gastrointestinal series, barium enema, myelography of the cervical and thoracico-lumbar regions, bone survey, electrolyte studies, acid and alkaline phosphatase studies, chest film, and electrocardiogram, were all normal. A plain film of the abdomen showed calcification of the abdominal aorta and its pelvic branches. A lumbar punc-

ture revealed clear fluid with normal manometric readings; the spinal fluid Wassermann and colloidal gold curve were negative and total protein was 72 mg/100 cc. Blood serology was negative.

The findings were characteristic of and compatible with diabetic myelodradiculoneuropathy. Of special importance is the marked atrophy of the shoulder girdle muscles, the deltoid and triceps. Of tangential interest in this case is the precipitation of the neuropathy following diabetic control (10), and the presence of severe depression accompanying the neuropathy (11).

There were five other cases with muscle atrophy of the proximal portion of the upper extremities. All had classical evidence of diabetic neuropathy including interosseous muscle atrophy of the hands, paresthesias, and numbness.

ASTHENIA (muscle weakness secondary to neuropathy). In four of our patients, loss of strength in the upper extremities was a major clinical complaint. The following case reports illustrate this:

Case I. A 57 year old woman with known diabetes for four years was admitted to the neurological service with complaints of numbness, tingling and increasing weakness of all extremities, particularly the hands, for the past eighteen months. She stated that she could no longer perform her routine housework with her arms and hands effectively. She also had noticed increased difficulty in walking as well as gradual decrease in sensitivity of the extremities. Pain had been present in the lower back region for the past eighteen months, increasing in severity. She further stated that she had sustained painless burns on her forearms as well as a painless burn on the tip of her right third finger while cooking. The diabetes had been under good control with strict dietary management.

On examination there was interosseous atrophy, particularly of the first interosseous space of both hands, the muscles of the forearms and the shoulder girdle. All deep tendon reflexes were absent. Pain sensation was impaired in all four extremities. There was absent vibratory sensation from the iliac crest down. There was diminution of sensation in a glove and stocking distribution of the extremities involving all modalities, namely pin-prick, touch, temperature, two-point discrimination, and vibratory sensation. There were several deep scars on the fingers, hands and forearms at the sites of previous burns. The blood Wassermann was negative. The spinal fluid Wassermann was negative and the total protein was 155 mg/100 cc. Blood urea nitrogen was 13 mg/100 cc; fasting blood sugar was 140 mg/100 cc. Chest x-ray was negative.

She was readmitted to the hospital four years later because of slow but continuous progression of her symptoms. In the interim she had been treated with repeated injections of Vitamin B₁ and Vitamin B₁₂ with no measurable beneficial effect. On this admission she stated that she was unable to walk without assistance, and, because of marked weakness of the upper extremities, was unable to put on her girdle. During this time she had again noted that in her now infrequent attempts at cooking she had sustained painless burns of the hands and forearms.

The general physical examination was non-contributory. The blood pressure was 150/90 mm Hg. The ocular fundi were normal. The scars of former burns were present in the upper extremities. Marked atrophy of the web muscles and interossei of both hands was present as on the previous admission; the leg musculature was normal. There was weakness of all four extremities, more distally than proximally. Discrete fine movements of hands were poorly performed with weakness of apposition and extension of all fingers. Sensation to pin-prick was diminished below the elbows and knees. There was loss of pain and temperature sensations in the hands and forearms, diminished vibration sense below the elbows and knees, and impaired position sense in the toes.

Laboratory: urine was negative for albumin and sugar; sedimentation rate, blood count, blood urea nitrogen, carbon dioxide content, chloride, sodium, potassium and cholesterol were entirely normal. Lumbar puncture revealed normal manometrics, clear fluid with no cells, and a total protein of 150 mg/100 cc; the Wassermann and colloidal gold curve were negative. The blood Wassermann was negative. Blood sugar ranged from 150 to 170 mg/100 cc. Electrocardiogram was normal and the electroencephalogram was within normal limits. The x-ray examination of the spine showed moderate hypertrophic spurring of the cervical, dorsal and lumbar spine. Myelogram was normal.

A muscle biopsy revealed some muscle fibers to be slightly atrophic and some fibers markedly so. In the latter areas the sarcoplasm formed irregular clumps containing clusters of bizarre and somewhat distorted sarcolemma nuclei. This change affected small groups of muscle fibers rather than isolated fibers. In some of these areas there was an increased quantity of fat. Pathological diagnosis was neurogenic muscle atrophy.

Electromyographic examination showed evidence of 1) denervation of the anterior tibialis muscles; 2) decrease in number of motor units, indicating neurogenic disease; and 3) abnormal conduction velocity of the nerves of the upper extremities. These findings were compatible with diffuse myeloradiculopathy and peripheral neuropathy.

This patient demonstrates loss of power of the upper extremities in association with atrophy of the involved muscles. The case also represents an instance of severe sensory impairment with painless burns (*vide infra*).

Case II. A 47 year old man complained chiefly of numbness in the tips of his fingers for the past six years. This was associated with marked weight loss during the previous year, and, for the previous three months, numbness and pain in the feet and weakness in both lower extremities. Three and a half years before he complained of dizziness and six months before he was discovered to have diabetes which was treated with diet and insulin, following which his dizzy spells disappeared.

Three months prior to admission he noted unsteadiness of gait. There was numbness and tingling of the hands and soles of the feet and shooting pain over both shins and the dorsum of both feet at night. Progressive weakness in the hands and fingers was associated with visible muscle wasting noted by the

patient. The hand and finger weakness so interfered with his ability to write or type for any period of time that he was forced to change his occupation.

Physical examination was negative except for a weak pulsation of the popliteal, posterior tibial and dorsalis pedis arteries. Neurologically, there was extensive bilateral atrophy of the interossei of the hands, the thenar eminences and the supra- and infra-spinatus muscles, and generalized atrophy of both lower extremities. The gait was unsteady and broadly based with a negative Romberg. The deep reflexes were one plus in the upper and absent in the lower extremities. The abdominal reflexes were absent. No pathological reflexes were obtained. There was glove-and-stocking hypalgesia below the elbow and knee with loss of temperature perception and vibration.

Gastric analysis and a gastrointestinal x-ray film series were normal. Lumbar puncture was normal except for an elevation of the spinal fluid protein to 62 mg/100 cc. The spinal fluid Wassermann and colloidal gold curve were negative. The blood Wassermann was negative.

This case is of particular pertinence since he had weakness, atrophy and neurological findings in the upper extremities. Also, the initial clinical manifestations of his diabetes were paresthesias and weakness in the upper extremities; this preceded the clinical diagnosis of diabetes by over five years (12).

Two other patients had weakness of the hands as a chief complaint. Each had the characteristic findings of diabetic neuropathy, negative serology, negative spinal fluid Wassermann and normal x-ray examinations of the spinal column. Briefly, one was a 59 year old physician who had had known diabetes for nine years. For the past five years there had been recurrent episodes of neuritis beginning with weakness in the lower and then spreading to the upper extremities. He was especially aware of the weakness in the hands because his hobby for many years had been cabinet work. Eventually he lost the power even to put in screws and was forced to abandon his hobby.

The other patient was a 41 year old man with diabetes of ten years' duration who, in addition to neuropathy with marked wasting of the interossei of both hands, had intermittent claudication, angina, and myocardial infarction. He complained of burning pain in the hands and feet with progressive weakness of the hands, especially evidenced by difficulty in holding objects. This weakness became so marked that he lost his ability to write and was unable to comb his hair.

Tensilon studies in the above cases were negative and therapeutic trials with drugs used beneficially in myasthenia were without effect.

SENSORY IMPAIRMENT. The clinical picture in this group was highlighted by the occurrence of deep, painless burns or other painless trauma. The similarity to tabetic syphilis in these cases is apparent and again points up the fact that these two conditions may simulate one another; this is clearly implied in the descriptive title "pseudo-tabes diabetica." Consequently, special care has been exercised to eliminate a possible luetic background as determined by history, blood serology, and spinal fluid serology. Such differential indices were uniformly established. There were five such patients in our series.



FIG. 5. Healing third degree painless burn.

Case I. A 65 year old male butcher had had known diabetes for thirty years, controlled by diet. During the course of his work he would on frequent occasions sustain cuts on his hands which were unaccompanied by pain. Foot baths were prescribed for the treatment of a toe infection; hot water was used and a painless, third degree burn of the foot ensued for which he required hospitalization. During the hospitalization, his hand slipped through the side-rails while he was asleep and came to rest on a radiator where it remained all night. The next morning there was a painless, severe third degree burn of the entire dorsum of the hand (Fig 5). This man had severe sensory loss involving the hands as well as the lower extremities. All deep reflexes were absent. He also had pupillary changes, impotence, and atrophy of the shoulder girdle, arms, thighs, and calves. Myelogram was normal. Blood serology and spinal fluid Wassermanns were negative. Spinal fluid protein was 126 mg/100 cc.

Case II. This 24 year old man developed diabetes seven years before. He

was receiving 72 units of NPH insulin daily with only fair control of his diabetes. He was admitted primarily for investigation of a one-year history of diarrhea associated with nocturnal fecal incontinence. Further history revealed that he had sustained frequent painless trauma to the skin of his lower extremities in the course of his work, which frequently included climbing ladders. He stated that there was numbness in both hands and feet and that several times he had fallen asleep with a cigarette in his hands and badly burned his fingers; these burns were entirely painless. He further stated that he had bruised his shins to the point of bleeding with almost no sensation. In addition, he complained of impotence, poor ejaculatory power and a definite diminution in frequency of voiding.

On examination he had moderately advanced bilateral diabetic retinopathy; blood pressure 125/90 mm Hg. There was a full thickness skin burn measuring one centimeter in diameter over the left index finger and a similar full thickness burn on the left middle finger; both of these had been painless and were due to cigarettes. The pupils were small and irregular. There were multiple bruises and scars on the lower extremities.

The skin over the lower extremities was dry and there was diminution of hair over the legs. Investigation revealed marked decrease of pain, pin-prick, vibratory and temperature sensation in a glove-and-stocking distribution; touch was blunted below the elbows and below the knees. The knee jerk and ankle jerk were absent. Laboratory serology of the blood and of the spinal fluid was negative. Lumbar puncture was entirely normal including manometrics, cell count, and a spinal fluid total protein of 26 mg/100 cc. A gastrointestinal x-ray series including small bowel, small bowel biopsy and malabsorption studies revealed findings consistent with and characteristic of diabetic enteropathy. Bladder investigation revealed the characteristic findings of a neurogenic vesical dysfunction.

This case is of special interest because of the presence of severe pseudotabes diabetica in a juvenile diabetic.

Case III. "Case II," detailed under the heading "Asthenia," represents deep, painless burns in association with advanced muscle weakness, both symptoms resulting from diabetic neuropathy.

There were two other patients with clear evidence of diabetic neuropathy and marked sensory impairment in the hands. In brief, one was a 60 year old man with diabetes of 10 years' duration. While adjusting the pilot light of his oven, he sustained a third degree, painless burn of the dorsum of the right fifth finger, proximal phalanx. In addition to absence of all deep reflexes, he had glove-and-stocking anesthesia.

The other patient was a 57 year old physician with diabetes of 15 years duration. In addition to other evidences of diabetic neuropathy (including peripheral neuropathy, diabetic enteropathy, neurogenic vesical dysfunction and impotence) he stated that when he sustained a cut of his hand or fingers, the only indication he had was the presence of blood—there was no associated pain.

Braille. Since blindness in the diabetic by virtue of cataracts, glaucoma, or retinopathy is so common, a significant number are eventually required to learn braille. It is an accepted experience by those who teach braille to the blind that the diabetic usually encounters more difficulty in mastering this skill than the non-diabetic. The difference is entirely independent of social, intellectual, cultural or educational background or motivation. In the light of our present findings, this may be traceable to the sensory impairment associated with diabetic neuropathy of the upper extremities, with impairment of the finer tactile sensations of the fingers.

RADICULITIS. We have observed three cases of cervical neuritis, two of which were unilateral and one bilateral in distribution. Mono-neuritis, or monoradiculoneuritis, has been described in the lower extremity. It is of interest to note that this can and does occur in the upper extremity. The following two cases represent instances of unilateral cervical neuritis in diabetics:

Case I. A 47 year old pianist with the chief complaint of weakness of the fingers of the left hand was a known diabetic of 13 years duration and had been taking 50 units of Protamine zinc insulin daily for the previous seven years with good control of the diabetes. Four months prior to admission he experienced moderately severe pain in the left scapular region which persisted for two weeks and then disappeared spontaneously. Following remission of the pain, the patient noted difficulty in using the fourth and fifth fingers of the left hand while playing the piano. Weakness rapidly progressed to involve all fingers of the left hand and was followed by wasting of the hand muscles.

On examination he was a well-nourished male in no acute distress. Blood pressure was 170/100 mm Hg. The general physical examination was within normal limits. The neurological examination disclosed normal mental status and no cranial nerve abnormalities. There was left wrist drop with marked weakness of all fingers of the left hand, most evident in extensor movements and involving the fifth finger to a greater degree. There was moderate weakness of the left triceps. The interossei and hypothenar muscles of the left hand were atrophied. No fasciculations were observed at any time. The left triceps reflex was depressed and there were no pathological reflexes. Sensory examination for all modalities was normal.

Laboratory examination revealed a normal blood count, sedimentation rate, blood urea nitrogen, total protein, albumin, globulin, cholesterol and radioactive iodine uptake. Urine contained a trace of albumin, traces of reducing substance and no formed elements. The fasting blood sugar was 158 mg/100 cc. Twenty-four hour urine contained 123 mg of creatine and 1417 mg of creatinine. Lumbar puncture showed normal manometric readings; the fluid was clear, colorless and contained no cells; the serology was negative and the total spinal fluid protein was 141 mg/100 cc. The blood Wassermann test was negative. The electrocardiogram revealed no abnormalities. X-ray films of the chest and skull were normal. X-ray film of the cervical spine showed moderate hypertrophic changes without narrowing of the interspaces; lumbosacral spine showed moderate narrowing of the lumbosacral and fourth inter-

space. Myelogram revealed no significant abnormality in the entire cervical-thoracic-lumbar region.

The normal myelography eliminated neoplasm; the normal urinary creatine-creatinine studies and normal thyroid studies eliminated a primary myopathy. It was therefore felt that this, in all probability, represented a cervical radiculopathy secondary to diabetes mellitus.

Case II. A 61 year old woman with diabetes of 15 years duration complained of severe pain beginning at the level of the left scapular spine and radiating to the left arm, with accompanying "pins and needles" sensation in the fingers. Because of the location of the pain, the possibility of an impending coronary thrombosis was considered and the patient was hospitalized for evaluation and observation. All tests of cardiac function (electrocardiogram, enzyme studies, etc.) were normal. Further observations including neurological examination indicated this to be a radiculitis associated with other manifestations of diabetic neuropathy. X-ray films of the cervical spine and serology were normal. Lumbar puncture showed normal pressure readings and a negative Wassermann; total spinal fluid protein was 58 mg/100 cc. It is of interest that the patient later developed classical, external ocular muscle palsy of the left sixth nerve which underwent spontaneous resolution in six weeks, as is characteristic of such diabetic neuropathic manifestations.

Case II. A 52 year old man had had diabetes for six years which was well-controlled with diet alone. He complained of pain in both upper extremities, the left greater than right, radiating from the cervical spine region. Examination revealed moderate atrophy of the muscles of the arm and forearm, absent reflexes of the upper extremities, and hyperesthesia of the hands, most marked in the left first and second fingers. There was absence of ankle jerk. There was no cervical spine tenderness. Lumbar puncture was entirely normal except for an elevation in the spinal fluid protein to 76 mg/100 cc. Wassermann test of the blood and spinal fluid was negative. Myelogram was normal. The pain was considerably worse at night but over the period of the next four months it cleared spontaneously. Of interest is the fact that shortly thereafter he developed impotence and a neurogenic bladder. Following surgery for the neurogenic bladder, he developed intense paresthesias of both feet which eventually cleared.

CLINICAL FEATURES

Age and Duration. Males predominated in a 2 to 1 ratio, there being 23 males and 12 females. The age distribution was overwhelmingly in the older group, 26 being over 60 years of age, although one of our patients was in the third decade of life; the oldest was an 83 year old man. Known duration of diabetes was a variable factor. For example, although 3 had had diabetes over 30 years and 6 for more than 20 years, 17 of our patients had had diabetes for 10 to 20 years and 9 had had it less than 10 years. Five patients were found to have the characteristic well-advanced wasting of the muscles of the hands at the initial diagnosis of their disease.

Lumbar puncture. This was performed in eighteen of these patients. In 15 of the 18 there was moderate elevation of the spinal fluid protein.

Control. Ten of the patients in our series were controlled with diet alone. Three of our patients were controlled with oral agents and the others required insulin. The insulin requirement ranged from 10 units to 100 units a day; ten of the insulin users required 40 units or less, whereas six required more than 40 units, two of these requiring 100 units a day. As to degree of control, this was roughly assessed as good-11, fair-6, poor-4, and in the remaining five, the diagnosis initially was made because of the characteristic atrophy of the hand muscles in conjunction with relatively inconspicuous carbohydrate metabolic disturbance.

Associated Neuropathic Manifestations. It must be emphasized that diabetic neuropathy of the upper extremities is only part of a more widespread involvement which almost invariably includes the lower extremities. The presence of severe atrophy of the interosseous muscles and other evidences of advanced peripheral neuropathy of the upper extremities were readily correlated with severe, advanced diabetic neuropathy as well as the syndrome of pseudo-tubes. Of our patients with well-marked evidence of diabetic neuropathy of the upper extremities, three had Charcot neurotrophic arthropathy, eight had severe atrophy of muscles in other parts of the body, eight were impotent, five had neurotrophic ulcers of the feet, six had diabetic entropathy, three had irregular pupils, four had gastric atony, three had orthostatic hypotension and seven had hypertension, eighteen had albuminuria and twenty had moderate to severe retinopathy. Several had severe peripheral vascular disease and three had gangrene sufficiently advanced to require local amputation.

Diagnosis. Diagnostic features are predominantly confined to the detection of the atrophy which may be a clue to the presence of diabetes, as described above, and sensory disturbances. Reflex abnormalities, specifically absent reflexes, do not necessarily have the same significance as in the lower extremity, although they are a valuable guide. Actually, this poses one of the difficulties in establishing the diagnosis of diabetic neuropathy in the upper extremities. The deep reflexes in the upper limbs, including the radial, ulnar, biceps and triceps, are at times difficult to elicit even in normal subjects. Furthermore, there is no method of reinforcing these reflexes. Thus, the inability to elicit reflexes bilaterally need not necessarily have diagnostic import if no other pathological signs are present. Hence, the diagnosis in these cases must be suspected primarily from other evidence such as muscle wasting, loss of power, and impaired sensory responses, corroborated by abnormal elevation of spinal fluid protein, and confirmed by abnormal electromyographic studies. Electromyographic studies in our patients were uniformly abnormal, documenting the presence of an underlying neuropathy. X-ray examination of the spine is mandatory and myelographic study is almost always indicated. The association with other manifestations of diabetes and diabetic neuropathy including visceral manifestations is most helpful. As previously

indicated, other neurological entities must be carefully ruled out (13). These include lues, progressive muscular atrophy, syringomyelia, lesions of the inferior roots of the brachial plexus, and lesions of the ulnar nerve (14). Two conditions require special mention since each is a "non-neurological" disease but may have interosseous atrophy of the hands as a conspicuous finding. Hypoglycemic neuropathy as occurring in pancreatic islet-cell adenoma frequently is evidenced by severe interosseous muscle atrophy of the hands (15) closely resembling that of our cases; the differential diagnosis on the basis of the differing carbohydrate metabolic abnormality is obvious. Recently, a case report of amyloidosis with protein abnormalities also exhibited this type and degree of atrophy (16).

Incidence. A routine survey was made of 200 unselected ambulatory office patients with diabetes to determine the incidence of neuropathy in the upper extremities and its frequency in relation to involvement of the lower extremity. Neuropathy was considered present if any motor or sensory impairment was elicited. Fifty-four of these patients had some neuropathic abnormality of the upper extremities, as compared with 146 instances of impairment present only in the lower extremities. Of the 54 with upper extremity involvement, 42 had minimal to mild involvement, whereas only 12 had clearly advanced neuropathy. Of the 146 with only lower extremity involvement, 78 had more advanced neuropathic involvement. Thus, although neuropathic involvement in the diabetic is more common and more severe in the lower extremity, the important point is that there is a significant and important number who do have involvement of the upper extremity. These figures obviously do not reflect the incidence of the severe, advanced abnormalities of the patients that form the basis for this paper.

CONCLUSION

It is evident from an appraisal of the case reports that diabetic neuropathy of the upper extremities has all the attributes and characteristics of diabetic neuropathy in any other location. Specifically, it can be the initial clinical presenting manifestation of diabetes, not necessarily related to the presence of overt hyperglycemia and glycosuria (12); it is not necessarily dependent upon control or duration of the diabetes (17). It is part of a more generalized neuropathic involvement in the diabetic syndrome and, as such, the common absence of the ankle jerk and its diagnostic significance should again be noted (18); finally, like absent ankle jerks, diabetic neuropathy of the upper extremities, especially the amyotrophic category, may be a clue in the diagnosis of hitherto unsuspected and undetected diabetes (19).

SUMMARY

This report documents the presence of diabetic neuropathy in the upper extremities, indicating its clinical significance and relative frequency of occurrence.

Its chief manifestations result from both sensory and motor neural im-

pairment. These include amyotrophy of the small muscles of the hand, most marked in the first interosseous space; asthenia; sensory loss; and radiculitis. It predominates in males and in the older diabetic population.

Diabetic neuropathy of the upper extremities is not necessarily related to control or duration of the disease and is usually associated with other manifestations of diabetic neuropathy, both somatic and visceral. It may be the initial clinical presenting manifestation of diabetes in the absence of overt evidences of impaired carbohydrate metabolism; as such it is a clue to the diagnosis of diabetes.

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Relationships of Recent Coronary Artery Occlusion and Acute Myocardial Infarction

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There is wide disagreement as to the relationships between recent coronary artery occlusion and acute myocardial infarction. The association of the two is reported as low (1) as 7% and as high (2) as 96%. While most authors believe that the majority of infarcts are caused by a coronary artery occlusion, there are some who are of the opinion that infarcts frequently occur without an arterial occlusion (3-5); and others who state that in instances of association of the two, the infarct may precede and cause the thrombus (6-10). This lack of consensus is particularly distressing as there is an urgent need for a well documented, definitive description of the relationship between recent coronary artery occlusion and acute myocardial infarction; and the necessary information could be gathered at autopsy by direct observation. Inasmuch as the differing studies were authored by experienced investigators, it was assumed that the problem was more complex than was apparent on casual inspection; and to develop the necessary expertise which would permit knowledgeable evaluation of the disparate reports, it was decided to examine prospectively the hearts from a large autopsy population and to reevaluate the conflicting claims.

MATERIAL AND METHOD

The author examined the hearts in a fresh state from 2500 consecutive autopsies in adults. The extramural branches of the coronary arteries were incised longitudinally with a sharp pointed, moderately heavy pair of scissors. The incision was stopped when the proximal tip of a thrombus was seen and the following two inches of unopened artery was removed as a block. If the distal incision traversed the thrombus, additional two inch blocks of unopened artery were removed until the lumen was free. All segments of severely calcified artery were also removed intact. The unopened segments of coronary artery (both those suspected of containing a thrombus as well as severely calcified segments) were fixed for 48 hours in 4% formaldehyde, decalcified for 24 hours in Decal* and then opened by a longitudinal incision along the midline with a new surgical blade. This effectively showed the topography of the thrombus and resulted in its division into two blocks which were much simpler to examine histologically than the multiple blocks and slides obtained from 2 mm spaced cross sections. The chambers of the heart were then opened in standard fashion, and the partially separated inter-ventricular septum and left ventricular wall were incised from apex to annulus in a plane parallel to the endo- and pericardium.

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The definition of acute myocardial infarction was limited to well-defined zones of necrosis at least 2.5 cm in greatest dimension and estimated to have occurred within one month of autopsy. Almost all of these infarcts were unifocal. This definition eliminated from consideration small zones of myocardial necrosis, practically always multifocal and most often subendocardial in distribution.

FINDINGS

Two thousand five hundred hearts were examined. Three hundred three acute infarcts were found in 292 hearts. There were 2 infarcts in each of 9 hearts and 3 in one heart. One hundred forty-nine infarcts were anterior or anterior septal; 116 were posterior; 30 were lateral; 6 were postero-lateral; and 2 involved the posterior portion of the interventricular septum and the contiguous right ventricle.

A recently occluded extramural branch of a coronary artery was associated with 278 (91.4%) of the 303 infarcts. The distal edge of the occlusions were always separated from the nearest edge of the infarct. The thrombi associated with anterior and anterior-septal wall infarctions were within 2 cm of the closest edge of the infarct in all but four instances; and in these the separation was 2 to 4.5 cm. In every instance of lateral wall infarct, the distal edge of the thrombus was within 2 cm of the nearest margin of the infarct. One hundred ten of arterial occlusions associated with posterior wall infarcts were in the right coronary artery and two were in the circumflex branch of the left. The distal edge of the thrombi was 2 to 6 cm distant from the nearest margin of the infarct in all but three instances of posterior wall infarct; and in these the thrombus was within 1.5 cm from the proximal edge of the infarct.

Two hundred fifty-five occlusions were seen upon gross examination, while 23 were recognized only after decalcification and longitudinal incision of a severely calcified segment of coronary artery. In seven instances, the lumen was occluded by a tan pink, gelatinoid thrombus. These were appreciated on gross examination after the author had been alerted to this possibility by examining a chance microscopic section through one. These thrombi were composed almost entirely of fibrin and were attached to an ulcerated focus of arteriosclerosis or were layered on an organizing but not occluding thrombus. They were all found in the narrowed lumina of severely calcified arterial segments.

Thirty-eight of the occluding thrombi were 3 mm or less in length. In two instances the occluding mass was a bolus of atheromatous debris extruded from an ulcerated arteriosclerotic plaque.

COMMENT

After completing the study of 2500 hearts, the differing reports were read once again; and it became apparent that all possible reasons for the differences in opinion as to the relationship between a recent coronary artery occlusion and an acute myocardial infarction could be considered in four general categories.

1. Differences deriving from geographic variables, this would include all environmental and genetic factors.
2. Differences deriving from temporal variables, the studies having been performed in different decades with the possibility that a change had occurred in the disease during the interim.
3. Differences deriving from variations in definition of recent occlusion and acute myocardial infarction.
4. Differences in material and method of examination.

Each category was considered successively. To minimize differences which might result from geographic variables, only studies which originated from the United States of America, Great Britain and Germany were evaluated. It was assumed that the populations of these countries showed sufficient similarity in their social, environmental and genetic backgrounds to cancel the potential variables from these sources. This restriction was not statistically significant as the overwhelming majority of the pertinent reports came from these three countries.

There was no evidence to support the possibility that differences in results could be due to a change in the morphogenesis of myocardial infarction over the years. The anatomic descriptions of 40 years ago (11) are the same as today. It may be, however, that a new or previously unappreciated mechanism is operative in the development of myocardial infarctions. If this were to obtain, then the differences in observed relationships should be clustered in different decades with a meaningful similarity in findings during the same decade. This is not so. Similarities and differences are well distributed in the reports over the past 40 years (1, 3, 6, 11, 17, 18, 19).

The definition of myocardial infarction as used in this study is admittedly arbitrary but approximates the concept of most pathologists, and describes the anatomic substrate almost always found associated with the clinical picture of myocardial infarction.

Inasmuch as the heart examined at autopsy was the material utilized by all authors and as all other possible reasons were eliminated, the only remaining source for the variations in results could be the differences which might result from the method of examination.

The methods of examining the coronary arteries consist essentially of an incision in the wall and inspection of the lumen; while the more sophisticated may employ an injection mass to visualize the arterial lumen. Most authors have developed an individual method using some combination of these approaches.

The use of an injection mass to visualize the coronary lumen does not offer any advantage. Although it is an excellent means of indicating sites of narrowing, the nature of the narrowing can only be determined by direct inspection; hence, incision of the wall with careful, direct examination of the lumen is sufficient and all other procedures are superfluous and may contribute to tissue distortion.

The longitudinal incision of a coronary artery is a simple, rapid and excellent method to examine a large number of coronary arteries routinely. It is

not used because of a widespread, but totally undocumented, opinion that the advancing tip of the incising scissors may dislodge a thrombus. This belief is in part based on the misconception that arterial and venous thrombi are identical and that arterial thrombi can be dislodged as easily as those within veins. There are, however, fundamental differences between the two. While a thrombus may form on an anatomically unblemished venous intima, and may be easily dislodged without leaving an obvious remnant; arterial thrombi form on, and are adherent to, an eroded arteriosclerotic plaque; and are not torn free by careful longitudinal incision of the arterial wall. If the artery is opened in an unnecessarily vigorous fashion, superficial fragments of the thrombus may crumble off; but an identifiable portion of the thrombus will remain attached to the ulcerated plaque. This is well illustrated by the many thrombi in the aorta; for despite the force of the arterial stream and the wide, pulsatile excursion of the aortic wall, these thrombi are infrequently dislodged en masse although superficial minute fragments may be swept into distal arterioles.

No matter which method of examining the coronary arteries is used, however, it must satisfy certain conditions. Calcified portions of the artery must be decalcified before incision of the tissue may be disrupted and the microscopic findings obscured; and the study of the hearts should be prospectively performed by an experienced examiner who is aware of the details of the problem. Reports based on retrospective studies of autopsy protocols are seriously flawed as these are written over many years by prosectors with different levels of experience, interest and ability.

The disparate reports under evaluation here were classified according to their definition of myocardial infarction and the adequacy of their method of examination. Those reports which did not contain sufficient data to permit a reasonable evaluation were not considered and the others were classified as Acceptable (2, 12, 13, 14, 16, 17, 22) or Unacceptable (1, 3, 4, 5, 9, 10).

The association of recent coronary artery occlusion and acute myocardial infarction ranged from 80% (1) to 96% (2) in the studies classified as Acceptable and from 7% (1) to 66% (5) in those called Unacceptable. There was no overlap between the groups. It would be most unlikely for this total correlation to be fortuitous; and it is reasonable to assume that it indicates a relationship between the definitions and methods of examination employed in the various studies and the results.

Ehrlich and Shinohara's paper (21) is a partial confirmation of the validity of this conclusion. They used two different definitions of myocardial infarction in a meticulously performed study. The myocardial lesion they called "unicentric" approximated the definition of myocardial infarction used in the present study; while the lesion they called "multicentric" did not. A coronary artery thrombus was associated with 17 of their 18 cases of "unicentric" myocardial infarction; while in 20 instances of "multicentric" infarction there were only two with an associated coronary artery thrombosis.

Further—the anatomic findings in the present study contradict the cur-

rently popular hypothesis that an acute myocardial infarct precedes and subsequently causes the formation of an associated coronary artery thrombus. Each of the thrombi in the present series were separated 1 to 6 cm from the closest margin of the associated infarct. If the infarct preceded and caused the thrombus, it would be reasonable to expect some of the thrombi to be directly contiguous to or even within the area of infarct. This was never seen. Furthermore, the topographic relationship of thrombus to infarct was so constant in instances of anterior and lateral wall infarct that this relationship was occasionally used to locate a thrombus. By an incision through the myocardium from apex to annulus and parallel to the endo- and pericardium, the most basilar border of the infarct could be easily located. The associated thrombus would then be found in the proximal 2 cm of the vessel subtending this area of infarction. This rigid topographic relationship between thrombus and infarct must indicate a causal event sequence; for if the thrombus had formed subsequent to the infarct, its location would be much more haphazard and would occasionally be found in one of the many other arteries circumscribing or within the infarction.

CONCLUSION

To determine the reasons for the lack of agreement in the many studies on the relationship of recent coronary artery occlusion and acute myocardial infarction, it was decided to examine a statistically significant autopsy population and with the completed experience as a background, to review the disparate reports.

It was concluded that the disagreements in these previous studies stemmed directly from the differences in definitions and methods of examination. Those studies which used acceptable definitions and methods reported an association of recent coronary artery occlusion and acute myocardial infarction in 80 to 96% of their cases.

The findings in the present study refute the assertions that an infarct precedes and subsequently causes the thrombus when the two are associated.

Fibrin thrombi as an occasional occluding mechanism in a narrowed and calcified coronary artery has not been previously described and merits a detailed study and report.

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Pediatric Aspects of Organelle Pathology of the Liver*

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I am most grateful for having been selected to give a lecture to honor Bela Schick. Any scientist would be proud to pay tribute to a man of Dr. Schick's achievements, particularly a member of the staff of Mount Sinai who can pay this to one of the great men who molded the heritage of this institution, the single strongest basis of the developing Mount Sinai School of Medicine. I am particularly elated to do so to a native of my birthplace, Vienna, where he was already one of the scientific leaders. In addition, there is a personal satisfaction in this opportunity for which I am grateful to my friend Horace Hodes because, as Dr. Schick has probably long forgotten, he was the first who introduced me, a refugee from Vienna, to The Mount Sinai Hospital in 1939. At that time, I told Paul Klemperer of the fluorescent microscopic demonstration of Vitamin A in tissues and Dr. Schick invited me to present this at the staff conference of the Department of Pediatrics. Months later, on his recommendation, I gave my first formal lecture in this country in the Blumenthal Auditorium (1). Little did I know when I traveled here from Chicago that almost 20 years later Mount Sinai would become my home. This tribute to Dr. Schick is, thus, an expression of my personal gratitude for contributing to the initiation of my own scientific career in the United States.

In this review of organelle pathology of the liver, I am surveying the work of my co-workers at this institution and I cherish, therefore, also this opportunity to express to these men my gratitude for their loyal cooperation in these last ten years. Their ideas and their work is what I am presenting.

To bring the keynote of this work in the Department of Pathology at The Mount Sinai Hospital into focus, it is worth remembering that the pathology of whole organs has been initiated by Hippocrates and Galen, the fathers of Western medicine. After Bichat and Benivieni localized disease into individual tissues, Giovanni Morgagni in his "De sedibus et causis morborum per anatomen indagatis" which appeared in 1761, crowned this effort so well illustrated in the new edition annotated by Paul Klemperer (2). This emphasis shifted in the middle of the 19th century to cellular pathology under the leadership of Rudolph Virchow. Much of the great progress of the last century in the biologic aspects of medicine resulted from this emphasis. As elaborate functional and structural techniques in recent years were applied to biologic processes, particularly to simple models exemplified by bacteria and viruses, molecular biology became the exciting frontier. Linus Pauling introduced the concept of molecular pathology when he demonstrated a variation in the amino acid sequence of hemoglobin as the basis of sickle cell disease. Mo-

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lecular pathology concerns alteration of processes on ultramicroscopic inter-phases where structural and functional alterations merge into one. Electron microscopy, at the highest resolution, is one of the effective tools. Between cellular pathology and molecular pathology, is a gap, not only on the level of magnification, which serves as the parameter of research, but probably more important on the level of communication between the biochemist and biophysicist concentrating on molecular and atomic processes and the classical pathologist concerned with dysfunction of organs and cells. In this gap malfunction of distinct cellular components, the organelles, is found. These are specialized units, endowed with defined functions. The organelles are self-perpetuating like viruses, but not self-sustained like cells. They carry out household activities for the cell or fulfill functions for the total organism. They represent cell compartments with membranes, mainly phospholipids, visualized with low resolution electron microscopy. Such studies which represent an extension of light microscopy have elaborated on the cellular pathology. For instance we learned that the Vitamin A containing cell shown to Dr. Schick and his group almost thirty years ago is a characteristic hepatic mesenchymal cell, the "lipocyte" (3), which, on electron microscopy, may be the long sought resting fibroblast of the liver (4).

Returning now to the specific alteration of the cellular organelles, and particularly to the embryonal organelle pathology, as it might possibly apply to the understanding of liver disease in children, we are confronted by the time-worn problem of the morphologist. This is the recognition of the meaning of variations in shape, whether observed with the naked eye, with the conventional microscope, or with the electron microscope. We have to remember that even electron microscopic alterations by themselves need not have more truly prognostic value than the study of the lobulations of the liver of sacrificial animals by the Babylonians who used them some 4,000 years ago as did the haruspices in old Rome to predict the future, such as the result of a war. If we do not wish to conduct haruspical electron microscopy, great as the inducement may be with a new tool, additional techniques such as histochemistry, immunocytochemistry, and particularly chemical analysis of cell fractions have to be applied.

Diffuse alterations of the liver in absence of necrosis were designated on the autopsy table as cloudy swelling. Little attempt was made to correlate this with altered function, though already some 40 years ago the German pharmacologist Hoppe-Seyler (5) emphasized a characteristic increase in protein content. In subsequent years, this diffuse injury of the liver was interpreted as toxic hepatitis and since World War II most such conditions, icteric and anicteric, were considered viral hepatitis, if no other cause was demonstrated. Today environmental factors are coming to the foreground as etiologic agents in children as well as in adults. Drugs and particularly fungal and plant toxins, for instance in the veno-occlusive disease in Jamaica (6), or in the childhood cirrhosis of India (7), are considered important causes of hepatitis and cirrhosis.

Since the liver is sensitive to oxygen want, as it occurs in the agonal period, and is rich in digestive enzymes, postmortal changes are extensive and prevent adequate evaluation. Liver biopsy appeared, therefore, a significant progress in recognizing cellular alterations during life as a useful mirror of functional changes. However, the years following introduction of liver biopsy, which was used for diagnostic purposes at The Mount Sinai Hospital as early as 1939 (8), brought disappointment. The correlation between even dramatic histologic changes and the results of the liver function tests was frequently hazy. Histologically, the impressive alteration, besides steatosis and scattered abnormal structures such as hyaline or acidophilic bodies, is necrosis of liver cells. However, this necrosis is by itself seldom widespread enough to produce a significant functional deficit. It is well known from physiologic studies that a large part of the liver has to be removed to produce a functional deficit. This hardly occurs in human liver disease except for full blown acute yellow atrophy. Statistical analysis in these years, however, revealed that the histologic feature best correlated with liver impairment was a subtle widespread change of viable hepatocytes which is characterized by diffuse variations in size and staining qualities of cytoplasm and nuclei (9). This is greatly influenced by histologic techniques and, thus, cannot be a reliable morphologic criterion. Electron microscopy, however, has established the nature of this change, spurious under the conventional microscope (10). When a rat receives carbon tetrachloride, fine structural changes are seen long before the histologic alterations are found or in zones which appear normal on conventional microscopy. Normal hepatocytes have membranous profiles, the endoplasmic reticulum which in part is lined by granules, the ribosomes (10, 11). These ribonucleoprotein granules are the site of cytoplasmic protein synthesis. They are aligned, as a rule, in spiral fashion as polysomes around the fine thread of messenger RNA, supposedly located between a smaller and a large ribosomal subunit. Along the polysomes activated amino acids carried by relatively small molecular soluble ribonucleic acids are combined to form the polypeptide chains of protein. Polysomes which are free in the cytoplasm are the sites of synthesis of structural proteins while synthesis of the proteins secreted by the hepatocytes occurs around those in contact with the phospholipid membrane of the endoplasmic reticulum. These latter proteins are albumin, alpha lipoproteins, coagulation proteins and some enzymes. The first recognizable damage of the hepatocyte is disruption of the granular endoplasmic reticulum with detachment of ribosomes. This is the diffuse lesion typically seen in man in viral hepatitis (12). It is functionally expressed in suppression of protein secretion from apparently viable hepatocytes as recognized experimentally in the delay of incorporation of radioactive amino acids (13). It is reflected clinically in the alterations of the serum proteins which are the basis of many hepatic tests. Steatosis of the liver, as it for instance occurs in the newly described children's disease of steatosis of liver and myocardium associated with brain changes (14), has many causes, not to be discussed here, but one of them, particularly in toxic liver injury, is the inhibition of secretion of

triglycerides as low density alpha lipoproteins. While other groups are studying the alterations of the ribosomes by biophysical techniques, we have been concerned with the disturbance of the membrane. Impairment of hepatocellular protein secretion and the subsequent lipid accumulation may be the result of three different processes: 1) disturbed synthesis of protein; 2) interference with the membrane associated assembly of complex proteins, such as glycolipoproteins, or with the combination of the apolipoproteins with the triglycerides (15); or 3) faulty release of the secretory product from the lumen, a "constipation," because of alterations of the phospholipid membrane, such as physical disruption or chemical oxidation of their unsaturated fatty acids. Indeed, under these circumstances, lipid droplets, so-called liposomes, can be seen within the altered endoplasmic reticulum.

Another site of injury is the mitochondrion, damage of which results in disturbance of oxidative phosphorylation, the source of energy for the cell. Only in few conditions are mitochondria the primary target, for instance, in oxygen deficiency, when they swell and increase in number. The same has been observed in our laboratory under increased oxygen tension, as used in space capsules (16). Morphologic changes with alteration of cristae is seen in cholestatic jaundice (17), and crystalloids are seen particularly in alcoholic injury even without other changes (18, 19). The functional significance of these mitochondrial changes is not established. The characteristic feature of alcoholic injury is the alcoholic hyaline, according to some a reflection of mitochondrial disturbance. It is interesting that the same feature is seen in acute stages of Wilson's disease (20), and peculiarly enough in Indian infantile cirrhosis. Its morphologic evolution from hepatitis to cirrhosis is identical to the alcoholic liver injury in the temperate zone. We are trying to discern the pathogenesis of the Indian disease using the hypothesis that it is a toxic injury of mitochondria.

The cell or plasma membrane may also be considered a specific organelle. The surface of the hepatocyte directed towards the sinusoidal space has many irregular processes or microvilli, which reflect the extensive exchange between cell and environment, probably mainly of electrolytes and water. In injury, water uptake is increased in the form of pinocytosis. This may cause swelling of the hepatocytes. Moreover, microvilli may disappear and cellular fragments may be seen in the parasinusoidal spaces. Whether this represents an intravital process or post biopsy breakage of an altered cell membrane is argued (17). Nevertheless, alteration of the cell membrane or probably of intracellular organelle membranes is the cause of the release of intracellular or intramitochondrial enzymes into the blood, the typical example being the transaminases. Their elevated activity in the blood is not a reflection of death of cells, as originally assumed, but rather of an alteration of living cells. This explains the rapid drop of the activity in massive hepatic necrosis. The extreme of the fluid loss of the hepatocytes is the acidophilic body, so frequently seen in viral hepatitis, which electron microscopically represents a lyophilized cell or a mummy (21).

Clinically even more important is the change of membrane of the bile canaliculus between two liver cells which is normally almost filled by microvilli. Both in extrahepatic biliary obstruction or in intrahepatic cholestasis, which occurs in infant and children liver diseases of various etiologies, the same electron microscopic alteration occurs, in that first the microvilli disappear and the canalicular lumen becomes dilated. However, the junctional complexes which seal the canaliculi remain intact and a widened pericanalicular zone is seen (22). The Golgi apparatus is also altered. In contrast to previous belief, cholestasis is not a primary obstructive disease of the biliary passages, but rather a change of the bile secretory apparatus of the hepatocyte, which may either be produced by pressure in extrahepatic biliary obstruction or by a primary metabolic change in intrahepatic cholestasis. This may be the only lesion, for instance, in some drug-induced injuries or in infantile cholestasis or it may be combined with alterations of the other organelles, which is conventionally designated as liver cell degeneration (11). Unfortunately, electron microscopy is not a diagnostic tool to separate them. Recent observations have thrown light on the nature of this metabolic defect. Evidence is accumulating that changes in the relative amounts of the different bile acids in hepatocytes may prevent the normal secretion of water and electrolytes into the bile, which is dependent on movement by bile acids. Administration of bile acids, like lithocholic acid, in excess of the amount normally present temporarily inhibits biliary secretion and produces the electron microscopic picture of cholestasis (23). The stagnation appears associated with accumulation of biliary material apparently in a matrix of cell surface mucopolysaccharides. On the basis of electron microscopy it appears that most types of cholestasis do not result from an intrahepatic mechanical obstruction but rather from a disorder of the hepatocellular organelles.

In this initial stage of organelle pathology we seem justified in distinguishing two types of organelle injury in viable hepatocytes. This might assist in clinical differential diagnostic considerations. One involves the group of organelles concerned with liver cell-blood relations, such as endoplasmic reticulum, mitochondria and perisinusoidal cell membrane. Disturbance here results in what we have called hepato-cellular degeneration or hepatic insufficiency. The other group of organelles is concerned with liver cell-bile relation and cholestasis is the result of malfunction of these (11). The varying mixtures of these two types of injuries of the hepatocytes explains the wide spectrum of clinical and laboratory manifestations in liver disease from pure cholestasis, as in early extrahepatic biliary obstruction or in exogenous or endogenous steroid induced jaundice to anicteric hepatitis. It also explains why more severe involvement of one group of organelles is associated with at least some damage of the other. The combination is found in most types of hepatitis of any etiology.

The organelle alterations discussed until now are catabolic in nature. However, just as in the response of the whole cell to injury, other processes are set in motion also on the level of organelles. Circumscribed damage of the cytoplasm of the individual cells can be repaired with preservation of the cell

itself in that altered organelles are segregated from the remaining cytoplasm by a membrane, and in the vacuole thus formed digestive enzymes accumulate. Acid phosphatase represents a convenient chemical and histochemical marker although its actual function is not established. It has, however, helped deDuve develop his lysosome concept of an intracellular digestive apparatus (24). The scavenger function is reflected in foci of cytoplasmic degradation (25) or autophagic vacuoles. Indigestible residues, mainly partially oxidized unsaturated fatty acids, become pigment bodies or lipofuscin, an indication of either previous injury or of old age of the cells, or in other words, a sign of turnover of organelles in persisting cells.

Hers (26) in deDuve's laboratory has also shown that some storage diseases result from congenital deficiency of lysosomal enzymes. Thus, in Hurler's disease, acid mucopolysaccharides accumulate in the lysosomes which become greatly enlarged (27), and similarly in type 2 glycogen storage disease of Pompe lack of lysosomal acid glucosidase results in excess glycogen accumulation in the lysosomes. Also, the giant cell response in hepatitis may in part be a lysosomal reaction, because these cells are loaded with pigment and lysosomes (28) although the mechanism of this reaction is not known.

Organelle regeneration, for instance, the development of new endoplasmic reticulum profiles around polysomes as typically in the fetus (29) is also found in regenerative nodules in cirrhosis.

In recent years much of the interest in the anabolic response of the liver has centered around the endoplasmic reticulum, particularly its smooth or agranular part. These tubular and vesicular structures increase upon administration of a variety of drugs in both experimental animals (30, 31) and in man for instance after administration of chlorpromazine. These phospholipid membranes are considered to be the site of a variety of drug handling enzymes. These have the transformation of preferentially lipid soluble products into water soluble ones in common and they are considered the site of detoxification. This seems to involve, not only exogenous substances, but also endogenous tissue breakdown products, because a similar excess of agranular endoplasmic reticulum is seen in liver disease such as viral hepatitis. The smooth endoplasmic reticulum is the site of many enzymatic processes which concern metabolism of steroid hormones, of sterols especially synthesis of cholesterol (32), and probably some chemical mediators. It is the site of the glucose-6-phosphatase activity responsible for the formation of blood sugar from glucose phosphate derived from glycogen. Bilirubin conjugation probably takes place here too. Enzyme induction involves additional synthesis and the enzymes induced are not necessarily related to the inducing substrate or its metabolites. Entirely unrelated enzymes are induced. Moreover, there are great individual variations in the pattern of enzymes induced, dependent on hormonal regulation, previous exposure and genetic factors. This is reminiscent of the response to an immunologic stimulus, an antigen, which results in production by lymphoid cells of the specific antibody and also of unrelated gamma globulins. The individual variations in pattern and the possible analogy of the organelle reaction with the cellular response in immunology has

led us to hypothesize, that the specific chemical nature and spatial arrangements of the fatty acids and nitrogenous bases in the phospholipids of the endoplasmic reticulum may determine the pattern of enzyme induction and thus represent a cytoplasmic code. This assumption is supported by morphologic and biochemical studies of alteration of the endoplasmic reticulum which showed disassociation between proliferated endoplasmic reticulum on one side, and enzyme activity and presence of the crucial hemoprotein on the other side.

My co-workers, in the last years, have attempted to separate the anabolic response of adaptation, beneficial to the individual, from a toxic effect (33). For instance, in the normal rat liver a moderate amount of agranular endoplasmic reticulum is associated with a given activity of a microsomal processing enzyme, aniline hydroxylase, and of a mitochondrial enzyme, proline oxidase. If small amounts of the pesticide dieldrin are given, the smooth endoplasmic reticulum increases parallel with a rise in aniline hydroxylase activity. If, however, the administration is prolonged, the excess endoplasmic reticulum persists, but biochemical and histological mitochondrial injury is noted and autophagic vacuoles appear, all of which we consider an indication of toxicity (34). A biphasic curve of enzyme activity exists with first increase and then depression. This can also be demonstrated, although with an initial phase of much shorter duration, with obvious hepatic toxins like butter yellow (aminoazobenzene). We assume that the initial increase of the endoplasmic reticulum is associated with hyperfunction. This represents adaptation, presumably by a feedback to nuclear DNA and messenger RNA. By contrast, excessive demands lead to hypertrophy with hypofunction which thus characterizes injury.

The new formation of endoplasmic reticulum is, however, only one parameter of the anabolic reaction. It is associated with increase in other cellular proteins and with enlargement of the liver as a whole. That liver injury may lead first to increased and subsequently to decreased protein synthesis reminds us of the old observation of Hoppe-Seyler (5) as to increased protein content in cloudy swelling.

Our group has been recently concerned with other aspects of injury as a result of anabolic reactions in the liver. Porphyria can result from excess hepatic synthesis of delta-amino-levulinic acid synthetase stimulated by administration of such drugs as phenobarbital (35). We are investigating the possibility that the cholestatic or hepatitic drug reactions occurring erratically in a few individuals exposed to the drugs (36) may also result from excess induction of some enzymes which damage the liver. This hypothesis is attractive because all drugs associated with erratic hepatic reactions are known to be strong enzyme inducers (33). For instance, the possibility has to be entertained that massive hepatic necrosis of the type of acute yellow atrophy following the administration of some drugs might result from excess induction of digestive enzyme in persons with a peculiar spatial configuration of the smooth endoplasmic reticulum.

Hypertrophy, that means enlargement of the cell without obvious hepatic

change, is only in part explained by the increased endoplasmic reticulum. It has to be separated from the new formation of cells or hyperplasia, which may be the result of reduced function of the organelles in viable cells. For instance, in the fatty liver, the fat-free cells may be arranged in several cells thick plates as an indication of regeneration (37).

Therefore, similar to the well known sequence in the reactions of whole cells changes in tasks, milieu or in regulators like hormones may result in an interplay also on the organelle level, which starts with a catabolic reaction or primary organelle injury. This may be followed by scavenger action or repair, then by regeneration with the formation of new organelles and by anabolic hypertrophy with enzyme induction. This may be a response to metabolic demands or to liver damage itself. It is, in turn, followed by new formation of cells. But this anabolic reaction may by itself, represent a new stress, potentially damaging the hepatocyte in the sense of a vicious circle or feedback amplification (10).

Before closing I would like briefly to contrast organelle pathology with the much better established cellular pathology. Hepatocytes, despite their deceptively simple structure under the conventional microscope, have a great variety of organelles engaged in many functions of the body. By contrast, the various mesenchymal cells, including those in the liver, such as macrophages, lymphoid cells, fibroblasts or leukocytes (38), each have only one main function. Changes in these cells belong to cellular pathology. This involves the field of immunology which was initiated by the concept of allergy introduced by Pirquet, Dr. Schick's co-worker was subsequently so ingeniously developed by Dr. Schick himself. For instance, plasma cells which form gamma globulin are demonstrable in the liver (39) and might be the site of formation of anti-ductular antibodies (40). The characteristic lesion in chronic active hepatitis, the piecemeal necrosis, is basically mesenchymal cell activation and thus reflects cellular pathology (41). Similarly, fibrosis and cirrhosis as a result of the action of fibroblasts represent cellular pathology or, if you wish, extracellular pathology because these reactions depend greatly on the life span of the extracellular collagen which can be determined by radioisotope techniques (42). The irreversible stage of hepatic fibrosis (cirrhosis) is the result of formation of collagen with a long life span (43). The concept of collagen diseases created in this institution by Paul Klemperer represents another example of extracellular pathology.

I have attempted to survey the development of organelle pathology as applied to the liver in a fashion which, I am sure, will soon appear naive. The attempt was made to go beyond picture book description of shapes or beyond haruspical electron microscopy and to point out the interplay of organelle reactions. There may be a few applications to the understanding of liver disease in children. These include the concept that the damage of viable cells determines the disturbance of liver function, that cholestasis is a disease of hepatocytes, that some storage diseases are congenital lysosomal disorders, that adaptation to stress can be distinguished from injury and that anabolic processes may be injurious.

I would like to return, in closing, to a historical thought. Cellular pathology as exemplified by the achievements of Dr. Schick and extracellular pathology by the work of Dr. Klemperer are today on a firm basis. As to the organelle pathology, I want to remind you of an old picture of Arabian and Italian anatomists who described that the spleen secretes bile into the stomach and the portal vein brings air to the liver. It took centuries to prove them wrong and it may take only a few years to show that much of what I have told you today is incorrect.

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Thrombotic Thrombocytopenic Purpura and Systemic Lupus Erythematosus

Report of a Case with Immunofluorescence Investigation of Vascular Lesions

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While the occasional concurrence of thrombotic thrombocytopenic purpura (TTP) and systemic lupus erythematosus (SLE) is well recognized (1, 2, 3) the nature of their relationship is not yet resolved. Disagreement still exists as to whether TTP represents a primary vascular disease or a disorder of coagulation. The case to be reported is that of a young girl who demonstrated the characteristic clinical and pathologic features of both SLE and TTP. Immunofluorescent studies demonstrated the presence of extensive intravascular deposits of fibrinogen and/or its derivatives, incompletely revealed by conventional histochemical stains for fibrin. The findings in this case support the concept that the so-called TTP+SLE syndrome represents a state of disseminated intravascular clotting superimposed on underlying SLE.

CASE REPORT

A 16 year old white woman was admitted to The Mount Sinai Hospital because of sore throat, fever and purpura. Five years earlier she had been first hospitalized for fever, arthralgias, and purpura, at which time several LE preparations were positive. Corticosteroid therapy was begun at this time, and was continued intermittently for the next five years. Shortly after the initial admission she developed an erythematous malar rash, along with repeated episodes of seizures and syncope. Two years prior to final admission she again required hospitalization for fever and purpura. Laboratory data during this admission included: hemoglobin, 12.5 gm/100 cc; white blood cell count, 5300/cu mm; platelet count, 20,000/cu mm; direct Coombs, 3+; indirect Coombs, 1+. Coagulation studies at that time revealed normal results, save for the low platelet count. The latter failed to improve on high steroid doses, and five months later a splenectomy was performed. This resulted in a prompt return of the platelet count to normal range. The resected spleen demonstrated, in addition to periarterial fibrosis consistent with SLE, occasional arteriolar thrombi, both fresh and organized.

She did relatively well until several weeks before final admission, when she again developed fever, extensive purpura, vaginal bleeding, and seizures. Babinski signs were present bilaterally. Laboratory data included; hematocrit, 30%; platelet count, 30,000/cu mm; ESR, 115 mm/hr, BUN, 24 mg/100 cc;

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albumin, 1.8 gm/100 cc; total serum cholesterol, 425 mg/100 cc; 24 hr urine, 4.5 gm protein/liter. On the 10th hospital day her right foot became cold, cyanotic, with absent pedal pulses. Despite intensive treatment, including exposure to hyperbaric oxygen, gangrene developed, requiring amputation of the right leg below the knee. The surgical specimen revealed a fresh thrombus in the posterior tibial artery, as well as recent and organized thrombi of medium sized veins, arteries, arterioles, and capillaries (Fig 1, 2). Outside the areas of frank gangrene (where the vessels were involved in a diffuse polymorphonuclear leukocytic infiltrate) there was no evidence of vascular inflammation or fibrinoid necrosis.

Peripheral blood smears now showed for the first time fragmentation of red blood cells, consistent with a microangiopathic hemolytic process. Serum cryoglobulins were absent, and plasma fibrinogen was 425 mg/100 cc. There was temporary improvement on high corticosteroid doses. However, one week later the hemoglobin suddenly dropped to 8.8 gm/100 cc without overt blood loss, the reticulocyte count rose, and the platelet count dropped to 42,000/cu mm, despite adequate bone marrow megakaryocytes. The peripheral blood smear revealed numerous burr and helmet cells (Fig. 3). She developed spiking fever, abdominal pain and distention, and died.

Necropsy, performed without examination of the central nervous system, revealed a young girl with Cushingoid appearance, extensive purpura, and

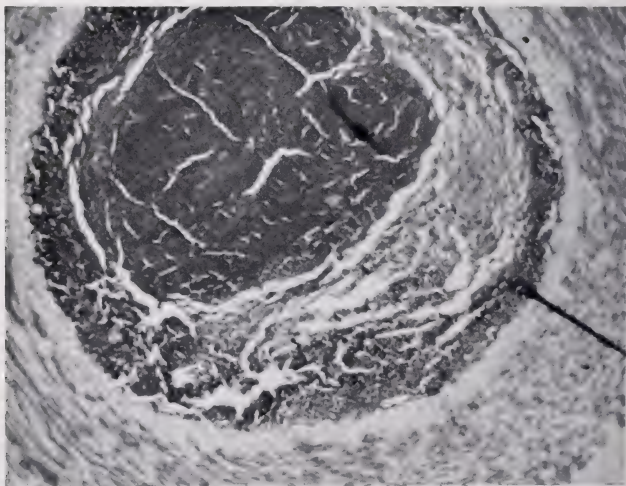


FIG. 1. Section of posterior tibial artery from amputated right leg demonstrating large fibrin thrombus without evidence of vasculitis (Lendrum's stain for fibrin (5), $\times 40$).

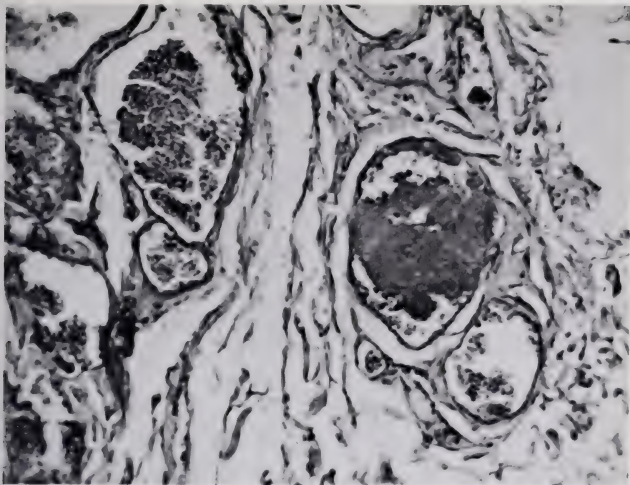


FIG. 2. Section from subcutaneous tissue of amputated leg revealing thrombus in venule (Lendrum's stain for fibrin. $\times 100$).

peripheral edema. The serous linings showed fibrinous exudates with moderate pleural and peritoneal effusions. Microscopic examination of the heart, liver, pancreas, adrenals, kidneys, and gastrointestinal tract revealed multiple "hyaline" thrombi in capillaries and arterioles. These thrombi frequently were lined along their luminal border with swollen endothelial cells, and appeared to be contiguous with the vessel wall (Fig. 4). The thrombi occurred frequently in association with focal parenchymal hemorrhages and necrosis. Occasional patchy areas of fibrosis suggested chronicity of the process. Severe hemorrhagic necrosis of the head of the pancreas was present, associated with multiple small vessel thromboses. The kidneys demonstrated, in addition to glomerular "wire loops," and fibrinoid necrosis characteristic of SLE, numerous thrombi in afferent arterioles (Fig 5).

The widespread "hyaline" capillary and arteriolar thrombi were stained strongly by periodic acid-Schiff (PAS) reagent but inconsistently and only patchily with conventional histochemical stains for fibrin (Fig 5). They failed to react with Alcian Blue reagent for acid mucopolysaccharide. Fresh frozen kidney and lymph node tissues were stained with fluoresceinated anti-human gamma G, gamma M, B_1C (complement), and fibrin* according to a previously described technique (6). Gamma G, gamma M, and B_1C globulins

*This term is used for convenience to describe fibrinogen and its derivative polymers including fibrin, which cannot be immunologically distinguished.

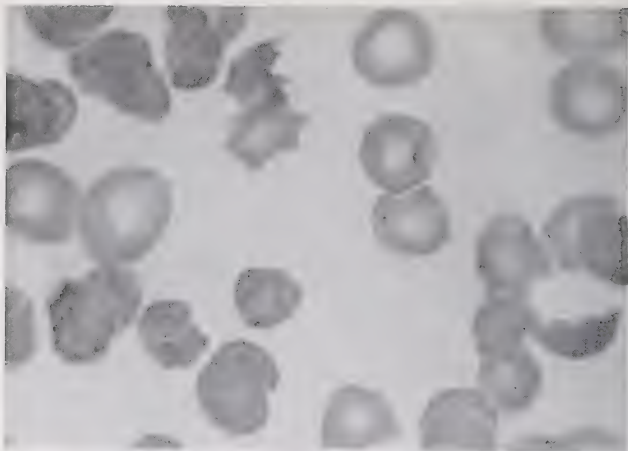


Fig. 3. Peripheral blood smear revealing numerous burr cells and a helmet cell (*lower right*) characteristic of a microangiopathic hemolytic anemia (Giemsa stain, $\times 1000$).

were thus demonstrated in significant concentrations in a beaded pattern along the basement membranes of glomerular capillaries (Fig 6). Fibrin was demonstrated in three distribution patterns in renal tissue; 1) along basement membranes, 2) within the mesangium, and 3) in intraluminal capillary and arteriolar thrombi (Fig 7). Lymph node arteriolar thrombi stained strongly for fibrin (Fig 8). There was no gamma globulin in the thrombus or vessel wall.

DISCUSSION

This case demonstrated the clinical and pathologic features of SLE, including the characteristic immunofluorescent gamma globulin pattern of lupus nephritis, as described by Paronetto and Koffler (6). In addition, the typical clinical and pathologic findings seen in TTP were present, including severe neurologic symptoms, a microangiopathic hemolytic anemia, and disseminated vascular thrombotic lesions, in this case involving large as well as small vessels. The pathologic findings suggested a low grade chronicity of the latter process with a terminal fulminating course.

The concurrence of these two relatively rare diseases was investigated by Levine and Shearn in 1964 (3). Out of 151 cases of TTP reported in the English literature up to that time they found 34 (23%) had features suggestive of SLE, consisting of either positive LE preparations or characteristic pathologic findings. Though unable to explain the pathogenetic relation be-

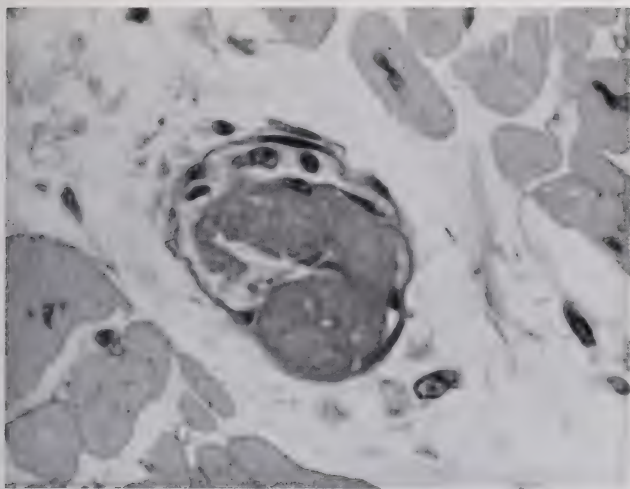


FIG. 4. Section of myocardium showing typical capillary thrombus. Note overlying swollen endothelial cells. (Periodic acid-Schiff, $\times 400$.)

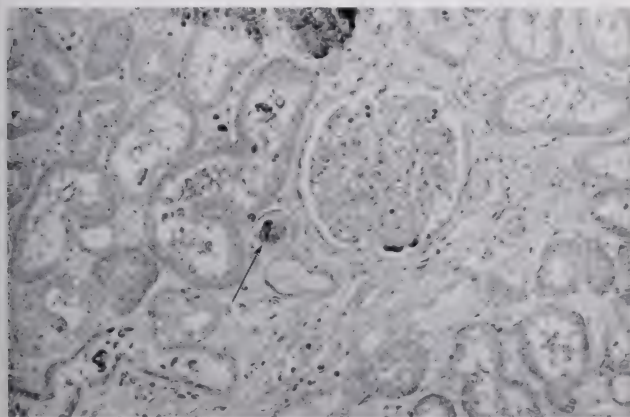


FIG. 5. Section of kidney stained for fibrin, demonstrating its presence in patchy strands (black) in glomerulus and afferent arteriole (*arrow*). Note typical "wire-looping" in glomeruli, characteristic of SLE. (Phosphotungstic acid hematoxylin, $\times 100$.)



FIG. 6. Cryostat section of kidney stained with fluoresceinated anti-gamma G globulin, showing distribution of this globulin in beaded pattern along basement membranes characteristic of SLE ($\times 250$).

tween the two diseases, they suggested that the syndrome TTP + SLE probably constituted an etiologically distinct subgroup of TTP.

Controversy still exists over the pathogenesis of TTP. Originally considered to be the result of widespread platelet thrombi by Baehr and Klemperer (7), it has since been ascribed to nonspecific endothelial injury causing platelet agglutination (8, 9), to hyperergic damage to vessel walls (10, 11), and to subendothelial deposition of an abnormal material, with associated disruption of the elastica and micro-aneurysm formation (12, 13, 14).

The frequent failure of the thrombotic vascular lesions to stain with conventional fibrin stains, and their common association with overlying swollen endothelial cells has led some investigators to postulate that the primary lesion of TTP consists of an abnormal vascular material, presumably elaborated by injured endothelial cells. Moore and Schoenberg (12) observed that these vascular lesions were PAS positive and occasionally exhibited metachromasia between pH 4.0 and 7.0. They suggested that this substance was an acid mucopolysaccharide elaborated by damaged endothelial cells, though they acknowledged that histochemically identical material occurs in platelets. The present study, however, failed to demonstrate acid mucopolysaccharide in these lesions by means of Alcian Blue staining.

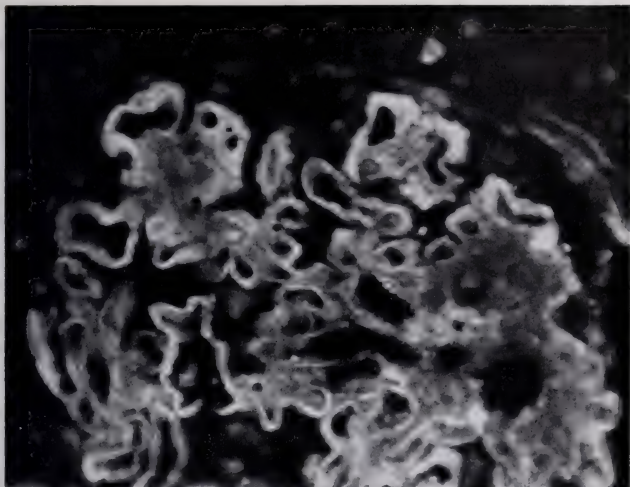


Fig. 7. Kidney section stained with fluoresceinated anti-fibrin, revealing the presence of this protein along basement membranes and within the mesangium, diffusely throughout the glomerulus. Compare with spotty distribution revealed histochemically in Fig. 5.

Present evidence, based on immunofluorescent and electron microscopic observations, indicates that the vascular lesions of TTP are comprised simply of fibrin. The recent studies of Feldman et al (15) demonstrated both intraluminal and subendothelial vascular deposits of this material in three cases of pure TTP, confirming the earlier findings of Craig (16). The present study demonstrates an identical picture in the syndrome TTP + SLE. The failure of these deposits to stain consistently with conventional histochemical stains may be explained by the electron microscopic findings of Vassalli and McCluskey (17) that thrombi of this type are often comprised of incompletely polymerized fibrinogen which has variable staining qualities.

What factors are responsible for the widespread fibrin deposits in pure TTP are not yet understood. There is suggestive evidence, however, that the pathologic picture of TTP seen in association with certain diseases of hypersensitivity such as SLE may be related to the Schwartzman Phenomenon. Vassalli and McCluskey (17) have produced widespread intravascular fibrin deposition, with associated swelling and proliferation of endothelial cells, similar to the changes seen in the present case, simply on stimulation of the coagulation mechanism by immune complexes.

McKay (4) has reviewed the evidence implicating circulating antigen-

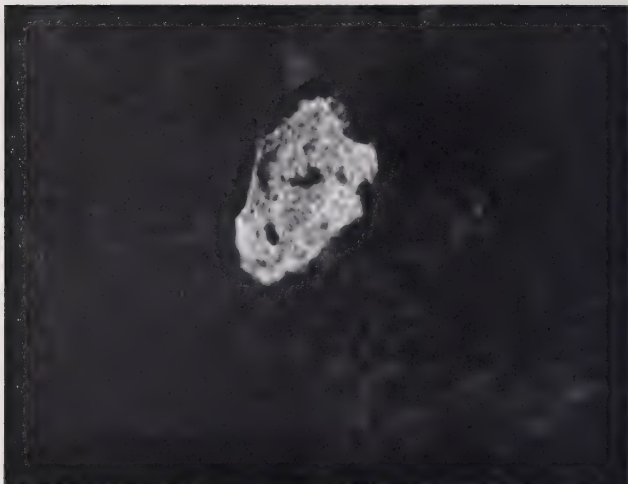


Fig. 8. Section of a peripheral lymph node stained with fluoresceinated anti-fibrin. An arteriolar fibrin thrombus is shown ($\times 560$).

antibody complexes as the factor responsible for the disseminated intravascular coagulation occurring in certain diseases of "hypersensitivity." He defined two clinical patterns: the first, a chronic progressive process, mainly characterized by glomerular deposits of fibrin; the second, a sudden, fulminating process, often superimposed on the first, with widespread thromboses of arterioles, capillaries and venules.

The present case clearly appears to conform to the latter category. The immunofluorescent demonstration of diffuse intravascular fibrin deposit adds further support to the concept that the syndrome SLE + TTP represents a fulminating form of a hypercoagulable state that may be common to many cases of SLE, as suggested by the frequent presence in that disease of glomerular fibrin (6, 18, 19). Whether those cases of TTP unassociated with SLE, which may be clinically and pathologically indistinguishable from the group TTP + SLE, are similarly the expression of a hypercoagulable state remains to be demonstrated.

SUMMARY

A case is reported of a young girl with the typical clinical and pathologic features of systemic lupus erythematosus (SLE) and thrombotic thrombocytopenic purpura (TTP), with the unusual finding of large vessel thromboses without vasculitis. Histochemical and immunofluorescent studies demonstrated

diffuse intravascular deposits of fibrin, supporting the concept that the syndrome SLE + TTP represents a disturbance of the coagulation mechanism, superimposed on the underlying SLE.

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Isoenzymes of Creatine Phosphokinase Determined by Acrylamide Gel Electrophoresis

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Creatine phosphokinase (ATP-creatine phosphotransferase, creatine kinase, ATP-creatine transphosphorylase) is the enzyme which catalyzes the reversible phosphorylation of creatine by adenosine triphosphate. There is significant activity of this enzyme in human skeletal muscle, cardiac muscle and brain tissue (1).

An increased serum creatine phosphokinase activity may reflect disease of these tissues and release of the enzyme from them. Recent work has established the finding that an elevated serum creatine phosphokinase is the most specific serum enzyme abnormality in Duchenne muscular dystrophy (2, 3, 4). Increased levels of creatine phosphokinase activity have also been observed in female carriers of this sex-linked myopathy (5). Other conditions in which elevations of the serum levels of creatine phosphokinase have been noted include the early stages of acute myocardial infarction and cerebrovascular infarction (1, 6, 7).

An electrophoretic display of enzyme activity is called a zymogram (8). The terms isozymes or isoenzymes refer to different protein components with similar enzyme activity as demonstrated by a particular histochemical method (9). Ultracentrifugal, chromatographic and electrophoretic techniques can be employed to resolve enzymes into different molecular forms. Differences between enzymes with the same substrate specificity have been found electrophoretically in different species, in different tissues from the same species and in adult and embryonic tissues (10-13).

It is the purpose of this report to describe a method utilizing acrylamide gel electrophoresis for separating isoenzymes of creatine phosphokinase in skeletal muscle, cardiac muscle, brain tissue and serum.

METHODS

Human biopsy specimens were obtained from the deltoid, biceps brachii, quadriceps femoris and gastrocnemius muscles. Specimens were also obtained from rabbit and cat skeletal muscle, cardiac muscle and brain tissue. The specimens were frozen rapidly in dry ice and stored at -25 degrees Centigrade. Extracts were prepared by homogenizing the specimens (50 to 100 mg) in ten volumes of 0.25 M sucrose, using a Potter-Elvehjem homogenizer. The homogenate was centrifuged at $20,000 \times g$ for 30 minutes and the supernatant used for electrophoresis.

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The apparatus employed for electrophoresis was the EC 470 vertical gel,* the method being a modification upon that of Raymond (14). The gels were prepared before each run by adding 0.2 ml of N,N,N,N'-tetramethylethylenediamine (TMED) and 0.4 gm ammonium persulfate to a filtered solution of 10 gm cyanogum in 200 ml of tris-buffer, pH 8.2, thus producing a gel of 5% acrylamide. The buffer contained tris(hydroxymethyl) aminomethane, 215.5 gm; disodium ethylene diaminetetra-acetate, 18.5 gm; and boric acid, 110.0 gm, in two liters of distilled water. The stock buffer was diluted ten times before use in the electrode vessels and for preparation of the gel. The buffer was recirculated to maintain a constant pH and composition. Twenty microliters of extract were applied to each trench formed at the upper end of the gel.

Water at 15° C. was circulated through the inner and outer plates. A direct current of 250 volts was applied, the effective voltage being 20 volts per centimeter, and the current 120 milliamperes at the beginning, and 90 milliamperes at the end of the electrophoresis. Total duration of the electrophoresis was 120 minutes.

Following electrophoresis the bands of creatine phosphokinase were visualized by staining in a solution containing adenosine-5-diphosphate sodium salt, 60 mg (0.001M); hexokinase, 300 microliters; glucose-6-phosphate dehydrogenase, 300 microliters; glucose, 60 mg (0.003M); magnesium chloride ($\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$), 210 mg (0.01M); nicotinamide adenine dinucleotide phosphate (NADP or TPN), 90 mg (0.0015M); MTT (3-(4,5-dimethyl-thiazolyl)-2)-2,5-diphenyl tetrazolium bromide, 48 mg; tris-buffer (0.05M), pH 7.4, 100 ml. Creatine phosphate, 150 mg (0.004M), is added to the solution as well as phenazine methosulfate (1 mg/ml), 2.4 ml. Incubation was maintained for two hours at 37 degrees Centigrade. A control solution was prepared in a similar manner, but creatine phosphate was not added. This method is an adaptation of the method for the biochemical determination of creatine phosphokinase as described by Oliver (15) and Nielsen and Ludvigsen (16).

RESULTS

Using acrylamide gel as the supporting medium, creatine phosphokinase isoenzymes characteristic of skeletal muscle, cardiac muscle and brain have been observed. The most anodic band has a mobility similar to that of albumin and is characteristic of brain CPK. Cardiac muscle creatine phosphokinase appears in the region of alpha-two globulin, while skeletal muscle shows a predominant band having a mobility between that of beta and gamma globulin (Fig 1). Serum contains one pink-colored band migrating commensurate with the brain band.

In addition to the "characteristic" band, brain tissue extract also manifests a band with the mobility of the heart muscle fraction. Heart muscle shows the band characteristic of "heart" and also the skeletal muscle pattern.

When creatine phosphate is omitted from the incubating solution, the bands

* E-C Apparatus Corporation, Philadelphia, Pennsylvania.

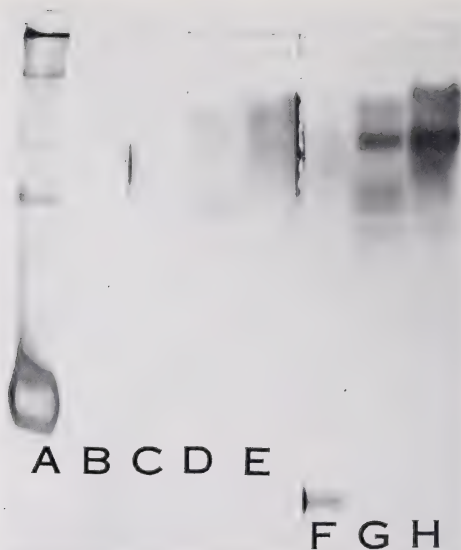


FIG. 1. Isoenzymes of creatine phosphokinase: A. Serum electrophoresis, amido-black stain. B. Electrophoresis of muscle extract, amido-black stain. C. Brain extract; creatine phosphate omitted from incubation fluid. D. Heart extract; creatine phosphate omitted from incubation fluid. E. Skeletal muscle extract; creatine phosphate omitted from incubation fluid. The diffuse bands represent unsuppressed myokinase activity. F-H. Brain, heart and skeletal muscle extracts, respectively; creatine phosphate included in incubation fluid.

do not appear. However, a diffuse band can sometimes be seen when the gel is incubated in this medium, migrating near the "heart band." This probably represents myokinase activity, and can be inhibited by including adenosine monophosphate (0.001M) in the incubation medium (17).

Samples of skeletal muscle and serum were studied from patients suffering from hereditary myopathies, such as the muscular dystrophies, the inflammatory myopathies, periodic paralysis and various neuropathic disorders. No characteristic differences were present in the patterns from the aforementioned patients as compared to "normal" human muscle. Moreover, the isoenzymes of cat and rabbit skeletal muscle resembled those of human muscle.

DISCUSSION

The studies described above indicate that creatine phosphokinase exists in several molecular forms. Deul and Van Breeman (18), using agar gel, observed one band derived from brain which had a greater electrophoretic mobility than

the single band of skeletal muscle. With heart tissue extracts, two bands were noted which were indistinguishable from those of brain and skeletal muscle as well as three others with intermediate mobility. Sjøvall and Voigt (19) described four bands using starch gel electrophoresis. However, with agar gel electrophoresis of muscle and brain extracts, only one band was noted, respectively, dependent on the presence of creatine phosphate. The bands moved in opposite directions.

The observations of Kar and Pearson (20), using agar gel, indicated that CPK from human skeletal muscle and heart could be resolved into three bands. Rosalki (21) studied the isoenzymes of CPK separated on cellulose acetate membranes. He found that cardiac muscle showed a major band between that of beta and gamma globulin. A minor component with a mobility of alpha-2-globulin was also noted. Specimens of "red" skeletal muscle showed the same pattern although "white" skeletal muscle revealed only the major isoenzyme band.

Using agar gel, Van Der Veen and Willebrands (22) demonstrated the existence of three isoenzymes of creatine phosphokinase. Pathologic muscles were not studied. However, they did detect two isoenzymes in the serum of patients with myocardial infarction and one or two of these isoenzymes in one patient with muscular dystrophy.

Studies of the ontogeny of creatine kinase isoenzymes in the rat brain, heart, and skeletal muscle, and in chicken skeletal muscle by agar gel electrophoresis revealed that three different bands are present in the adult animal (23). In adult animals the brain isoenzyme (I) migrates toward the anode. Skeletal muscle and heart showed a cathodic migrating band (III) while the heart tissue also showed a band of intermediate electrophoretic mobility (II). During the early stages of ontogeny, only isoenzyme I was present in the organs. This band disappeared slowly in skeletal muscle, being replaced by isoenzymes II and then III. The adult pattern was reached about 90 days after birth in the rat and at hatching in the chicken. Heart muscle manifested a similar transition but the changes commenced earlier and remained stationary at the isoenzyme II and isoenzyme III stage. Brain tissue possessed isoenzyme I throughout life.

Acrylamide gel is a good medium for demonstrating the isoenzymes of creatine phosphokinase. Although the aforementioned results are at variance with some of the findings of other investigators, this may represent differences in methodology regarding type, pH and ionic strength of the buffer, and temperature and duration of electrophoresis. However, the presence of skeletal muscle, brain and cardiac muscle isoenzymes has been ascertained.

In contrast to the changes in the isoenzymes of lactic dehydrogenase in patients suffering from myopathic and neuropathic disorders, no characteristic trait in the CPK patterns was noted in these patients.

SUMMARY

The isoenzymes of creatine phosphokinase have been studied using acrylamide gel as the supporting medium. The existence of specific patterns for

serum, brain, skeletal muscle and cardiac muscle were noted. The samples from patients with neuropathic and myopathic disorders showed no characteristic changes from that observed in normals.

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Buccal Androsterone Therapy of Hirsutism: A Preliminary Report

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Studies have directed attention to potential biologic properties of hormonal metabolites which may be unlike or antagonistic to those exhibited by their precursor hormones. (1) Such examples include the observation of the thermogenic properties of etiocholanolone (2) as well as the cholesterol, triglyceride and phospholipid lowering effects of esterified androsterone (3-6). It is conceivable that physiologic interaction of the precursor hormone with its *in vivo* metabolites may affect expression of hormonal action in man (1). This system may preserve homeostasis by allowing for a feed-back mechanism.

Testosterone has been suggested as the androgen responsible for the growth of facial and body hair in some patients with "idiopathic" hirsutism (7). Elevated levels of plasma (8, 9) and urinary testosterone (10) have been described since in many of these subjects. Investigations of patients with hirsutism of varying etiologies (11-16) have frequently demonstrated increased levels of urinary conjugated androsterone, a metabolite of three potential hirsutism-producing hormones; testosterone, androstenedione and dehydroepiandrosterone. Androsterone, although not secreted by the adrenal or gonad, is considered to be a mild androgen on the basis of animal experiments (17). However, the observation of conjugated androsterone in the urine of normal non-hirsute women, at times in greater quantities than in normal males (18-20), suggested a disparity in the attempt to relate hirsutism to urinary androsterone level.

The purpose of this communication is to report the use of a buccal preparation of unconjugated androsterone in the treatment of hirsutism and its effect upon the urinary excretion of testosterone and epitestosterone.

MATERIALS AND METHODS

The clinical material is summarized in Table 1. All nine patients had been shaving their face regularly and had marked beard growth. They received a placebo dose of inert buccal tablets for four weeks prior to instituting buccal unconjugated androsterone* and reported no improvement. Buccal administration was selected to avoid the rapid liver conjugation of androsterone which otherwise might occur with oral administration. A divided dosage of five 50 mg buccal tablets daily was selected for this purpose. The buccal route produced adequate absorption of androsterone as demonstrated in the urinary steroid chromatograms** of patients E.S. and D.S. (Table 2). Improvement

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* Formula of the buccal tablet- Androsterone...50.0 gm per 1000 tab., Polyethylene Glycol 6000...149.0 gm per 1000 tab., and Magnesium Stearate...1.0 gm per 1000 tab., kindly supplied by Dr. Jack Black, Schering Corporation, Bloomfield, N.J.

** Performed by Bioscience Laboratories, Van Nuys, California (21)

TABLE 1

Nine Hirsute Females Treated with Buccal Androsterone 50 mg Five Times Daily or 250 mg Four Times Daily

Patient	Age	Diagnosis	Results	Comment
1. E.S.	47	I.H.	I	Twice daily shaving, decreased to every other day. Increase of dosage to 250 mg q.i.d. did not alter the improvement.
2. D.S.	32	I.H.	I	Daily shaving of face, decreased to every 2-3 days.
3. R.K.	28	I.H.	I	Daily shaving of face, decreased to every other day.
4. N.D.	56	I.H.	I	Daily shaving of face, decreased to every other day.
5. S.S.	27	S.L.	I	Once weekly shaving decreased to once every 3-4 weeks.
6. L.R.	38	D.L.	I	Once weekly shaving decreased to every 2-3 weeks.
7. S.L.	32	S.L.	F	No improvement of daily shaving even with an increase of dosage to 250 mg q.i.d.
8. J.M.	35	S.L.	F	No improvement of daily shaving even with an increase of dosage to 250 mg q.i.d.
9. J.K.	38	S.L.	F	No improvement of daily shaving even with an increase of dosage to 250 mg q.i.d.

Key: I.H.—Idiopathic Hirsutism

S.L.—Stein-Leventhal

D.L.—Diffuse Luteinization of Ovaries

I—Improved

F—Failure

TABLE 2

Urinary Steroid Chromatograms before and during Buccal Androsterone Therapy in Two Females with Idiopathic Hirsutism*

Steroid	Normal values	Patient E.S. (age 47)		Patient D.S. (age 32)	
		5/1/61 Control	8/1/61 On 500 mg/d	10/21/61 Control	1/22/62 On 250 mg/d
Total Crude 17 KS.	6-15	8.3	59.0	6.6	35.0
Dehydroepiandrosterone	0-2.5	0.1	1.4	0.2	0.4
Etiocbolanolone	0.8-4.9	1.1	4.1	1.1	1.6
Androsterone	0.5-3.7	0.8	45.0	1.6	24.4
11 β OH Etiocbolanolone	0.2-1.7	0.4	1.7	0.1	0.3
11 β OH Androsterone	0-0.5	0.2	1.6	<0.1	0.2
11-keto-Etiocbolanolone	0.3-1.2	0.3	1.4	0.1	0.2
11-keto Androsterone	0.0-2.4	0.1	1.7	<0.1	0.2
A/E Ratio	0.3-1.4	0.7	11.0	1.4	15.3
17-OHCS (Glenn Nelson)	2.0-6.0	4.4	3.0	2.8	1.3
Pregnanetriol	Up to 4.0	3.9	1.4	2.5	

* Performed by Bio-Science Laboratories, Van Nuys, California and expressed as mg/24 hours.

was gauged by the patient's decrease in regular requirement for shaving and by facial photographs taken 24 hours after shaving. Urinary testosterone and epitestosterone determinations were performed by the method of Futterweit, et al (10, 22, 23). The method involves thin-layer and gas-liquid chromatog-

TABLE 3

Suppression of Urinary Testosterone and Epitestosterone Glucuronide by Buccal Androsterone 250 mg/d for 1 month*

Patient	Age	Sex	Diagnosis	Testosterone and epitestosterone glucuronide ($\mu\text{g}/24 \text{ hr}$)	
				Control	During treatment
1. a-E.S.	47	F	Idiopathic Hirsutism	47	2
b-E.S.	48	F	Second Suppression 1 Year after Therapy Halted	57	4
2. E.O.	29	F	Idiopathic Hirsutism	102	13
3. M.S.	24	F	Idiopathic Hirsutism	54	10
4. A.C.	40	M	Bilateral Adrenalectomy	92	23

* Values for normal males (age 19-29 years, 65-348); (age 30-40 years, 45-178); normal females (age 10-53 years, 2-10) (10).

raphy employing C-1, 2-3 H-testosterone as a tracer. The normal levels of the combined urinary excretion of testosterone and epitestosterone glucuronide in normal adult females varies from 2-10 $\mu\text{g}/24 \text{ hr}$, with a mean excretion of 6 μg (10).

RESULTS

A definite decrease in shaving requirement was noted in six patients following 3 to 4 weeks of buccal androsterone administration (Table 1). The benefits obtained within four months did not progressively increase with continuation of treatment for periods up to 18 months. In no patient, however, was there total cessation of beard growth. Following discontinuation of treatment the beard growth gradually returned toward the original frequency of shaving. Three patients failed to demonstrate any significant improvement. Other than the bitter taste of the buccal tablets there were no adverse effects of the medication. Specifically there was no change in menses, libido, appetite, weight or blood pressure. One patient (R.K.) became pregnant while on therapy and the drug was discontinued in her second month of gestation. She delivered a normal male child at full term.

Studies of urinary testosterone and epitestosterone glucuronide excretion were performed in three females with idiopathic hirsutism and elevated basal urinary androgen metabolite levels. One patient (E.S.) was studied twice. After one month of buccal androsterone therapy the urinary testosterone and epitestosterone glucuronide levels were markedly decreased in these subjects (Table 3). In addition, a bilaterally adrenalectomized male (A.C.) was given buccal androsterone for one month and also demonstrated a marked decrease in these urinary androgen metabolites.

DISCUSSION

The studies described are of particular interest in view of the report by Davis et al (24) who demonstrated suppression of testosterone production in

males with physiologic doses of androgen 2-a-methyl-dihydrotestosterone. The androgen was considered to be suppressing the interstitial-cell stimulating hormone secretion of the pituitary gland. Zarate et al (25) administered an anti-androgen, 17-a-methyl-b-nortestosterone, to 28 women with idiopathic hirsutism and noted lessening of the hirsutism in 20. Our observation of a decrease of urinary testosterone and epitestosterone levels in four subjects receiving buccal androsterone suggests that free androsterone may participate in a feed-back mechanism which attempts to block or modify excessive endogenous production of active androgen.

SUMMARY

Six of nine subjects with hirsutism of various etiologies (idiopathic hirsutism, Stein-Leventhal syndrome and diffuse luteinization of the ovaries) demonstrated clinical response to a buccal preparation of unconjugated androsterone. Three females with idiopathic hirsutism and an adrenalectomized male subject demonstrated a marked decrease in the urinary excretion of testosterone and epitestosterone glucuronide while receiving the androsterone preparation. The physiological implications of these findings are briefly discussed.

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CLINICO-PATHOLOGICAL CONFERENCE

Fever, Hepatosplenomegaly and Pulmonary Densities

Edited by

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A 62 year old Venezuelan housewife was admitted because of fever, chills, weakness and a 20 pound loss in weight.

Seven weeks prior to admission she developed fever, chills and night sweats. On admission to the hospital in Venezuela, the liver and spleen were enlarged. An oral cholecystogram, intravenous pyelogram, barium enema and upper gastrointestinal examinations were reported as normal. She was treated with multiple antibiotics without improvement and was transferred to The Mount Sinai Hospital for further evaluation.

There was no antecedent upper respiratory infection, nausea, vomiting or contact with tuberculosis.

She was acutely ill. The blood pressure was 130/80, pulse 84/min, respirations 16/min, and temperature 104°F. Her head and neck were normal except for a 1 cm freely movable node in the left supraclavicular fossa. Scattered rales were heard in the left posterior lung field, and the heart was normal. The liver and spleen were palpated 4 cm below the costal margin. The neurologic examination was normal. The hemoglobin was 10.9 gm/100 cc, the white blood count was 4,100/cu mm with 66% segmented leukocytes, 19% band forms, 10% lymphocytes, 4% monocytes, and 1% eosinophils. The erythrocyte sedimentation rate was 62 mm/hr, and the platelet count was 200,000/cu mm. The blood urea nitrogen was 12 mg/100 cc, the fasting blood sugar 106 mg/100 cc, and alkaline phosphatase activity 7.9 Bessie-Lowry units. The serum bilirubin, prothrombin time, and transaminase activities were normal. The serum albumin was 2.39 gm 100 cc, alpha₁ globulin 0.55 gm/100 cc, alpha₂ 0.639 gm/100 cc, beta 0.479 gm 100 cc and gamma 2.59 gm 100 cc. There was slight proteinuria and the urinary sediment contained 6 to 10 white blood cells per high power field. Several blood cultures were sterile. Monotest, latex fixation, LE preparation and febrile agglutinin studies were negative. An x-ray film of the chest revealed nodular densities throughout both lung fields and distortion of the pulmonary markings. An intravenous pyelogram and x-ray examination of the skeleton were normal. Skin tests for histoplasmosis, blastomycosis, coccidiomycosis and tuberculosis were nonreactive. A stool examination for ova and parasites was normal. She continued to have temperature elevations to 104°F. A bone marrow examination and biopsy of the liver were performed. She became jaundiced, and the liver and spleen were noted to be larger. The serum alkaline phosphatase was 20.8 Bessie-Lowry units. Ascites and peripheral edema developed and she became disoriented. She expired on the 38th hospital day.

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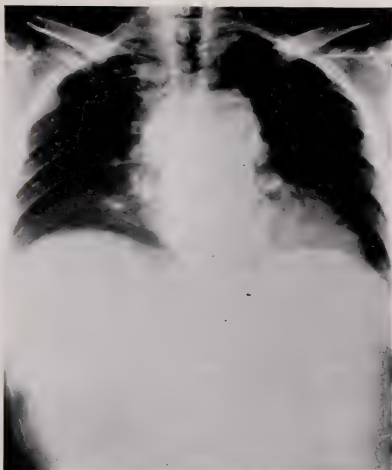


FIG. 1. Chest X-ray showing extensive calcification of the posterior mediastinal nodes.

*Dr. L. E. Siltzbach**: This patient had a fatal febrile illness of some 12 weeks duration unresponsive to the ordinary antibiotics. She had peculiar nodules in the lungs, and negative skin tests to the ordinary delayed type antigens. The lymph nodes in the posterior mediastinum, and the retro-peritoneal area showed calcification of the entire node substance (Fig 1). The two most common causes of such calcification would be tuberculosis and histoplasmosis.

The possibility of gallbladder disease was considered in Venezuela, probably because she had a palpable liver. They also looked for a liver abscess, particularly an amoebic abscess. However, nodules in the lung present here are incompatible with a spreading amoebic abscess.

The enteric and febrile agglutinins were negative and therefore typhoid and salmonellosis would be unlikely as a cause of the fever. In addition, the liver and spleen were quite large and nodular lesions in the lungs are not usually part of the amoebic infections.

Similarly, I need not consider such conditions which may be common in areas of Venezuela like malaria or other parasitic diseases. There was no eosinophilia or identifiable parasites. Deep fungal infections can certainly produce this state but I do not know how to prove the diagnosis without some focalizing area of involvement. Remember, this patient had no respiratory or

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gastrointestinal symptoms. As a matter of fact, except for the fever and night sweats, the constitutional signs were surprisingly minimal. A bone marrow examination and biopsy of the liver apparently revealed significant abnormalities and the results of these examinations are being withheld.

One should certainly consider an infectious cause of the fever such as tuberculosis. I will return to this consideration shortly. Other causes of fever include tumors. Hypernephroma which metastasizes to the lung produces fever and it is possible that the patient had some liver damage prior to the onset of her illness. However, there is no irregularity or elevation of the right dome of the diaphragm. Pancreatic and lung tumors also occasionally give fever but there is no supporting evidence to make these diagnoses either.

Lymphoma is sometimes a very difficult diagnosis to establish. Hepatosplenomegaly, peripheral node enlargement, unremitting fever are characteristic but nodules in the lung *without* mediastinal adenopathy is an uncommon finding in intrathoracic Hodgkin's disease. Generally, by the time there are nodulations in the lung, mediastinal adenopathy is also present although there are exceptions to that rule. I am not satisfied with a diagnosis of lymphoma particularly because the constellation of symptoms does not quite fit. I would have expected the patient to be more anemic or to have significant peripheral lymphadenopathy. On the other hand, I cannot exclude the diagnosis of disseminated lymphoma with involvement of the liver producing jaundice, either by lymph nodes compressing the common duct, or more by direct lymphomatous involvement of the liver.

I have already, more or less, dismissed gallbladder disease and I don't believe she had suppurative cholangitis or a pyelophlebitis since she did not show any tenderness or focalizing signs in the right upper quadrant. Nor do I think she had a hepatic abscess or metastatic tumor in the liver. Although geographically, coming from Venezuela, she probably would be more likely to contract amebiasis (11 per cent of the population of the United States have *Entamoeba histolytica* in their stools), she had none of the physical or laboratory features.

I am also unable to rule out the possibility that the findings which were present during her recent illness and which brought her death actually preceded her illness. She could, for example, have had a postnecrotic cirrhosis and her death may then have resulted from liver failure. Since jaundice came rather late in her illness, a drug may have been responsible. We are not told what drugs were used but drugs such as paraaminosalicylic acid and isoniazid used in the treatment of tuberculosis, or diodoquin in the treatment of amoebic dysentery may produce jaundice. If paraaminosalicylic acid was responsible and was administered to the patient perhaps three weeks or more before her death, this could explain some but not all of the clinical findings.

Finally, the patient could have had miliary tuberculosis, in spite of the negative tuberculin test. Patients with miliary tuberculosis may not react to tuberculin although contrary to the general impression, most commonly do react to tuberculin. When one does not obtain a positive tuberculin reaction in

miliary tuberculosis, it is worrisome. In the cachectic patient, or one dying in uremia, or in patients with lymphoma or sarcoidosis, the tuberculin test is often negative. On the basis of what we are given, I would be willing to assume that this patient had tuberculosis in spite of the negative tuberculin reaction because of the calcified lymph nodes in the posterior mediastinum. The patient also had a negative histoplasmin test.

In Venezuela in 1936, the death rate from tuberculosis was 243 per 100,000. This woman was born in 1906, at a time when the tuberculosis death rate was close to 550 per 100,000. She could then easily be exposed during her lifetime to many tuberculosis patients. By 1962, the death rate for tuberculosis had dropped in Venezuela, as it had all over the world, from 20 to 14 per 100,000. In the United States it was less than 5 per 100,000 in that year.

I am not so concerned with localized pulmonary tuberculosis as I am with extrapulmonary tuberculosis in this patient. If we inspect the statistics in Venezuela of deaths from extrapulmonary tuberculosis in the year 1960, there were 2.1 per 100,000 deaths whereas in the United States it was only 0.4 per 100,000 deaths. Therefore, the incidence of deaths from disseminated tuberculosis in Venezuela is about five times as great as it was in the United States. With that epidemiologic background, in spite of the negative tuberculin skin test, this woman, I believe, could have had miliary tuberculosis. According to Dr. A. R. Rich, pathologically miliary tuberculosis should include a minimum of three organs—lung, liver and spleen, all of which could be present here. She had hepatosplenomegaly and nodules in the lung. I must admit that the nodules in the lung were not those usually seen in miliary tuberculosis. They were not of miliary size, not universally distributed, nor were they more dense or larger in the upper lobes. However, occasionally disseminated tuberculosis is not a granulomatous or a productive inflammatory process. There may be predominant areas of necrosis and in some, when there is acute dissemination, the lesions are attended by little response in terms of epithelioid cell tubercle formation. This nonproductive form of hematogenous tuberculosis is common in debilitated children and the aged.

In the absence of information regarding the liver biopsy, my diagnosis, therefore, is a patchwork because it suggests that the jaundice may best be explained by an exogenous cause rather than by the disease itself. This exogenous cause may have been a sensitivity to a drug used in the course of her treatment which I think may have been miliary tuberculosis. Obviously, a patient with high fever who does not respond to antibiotics may well have been getting antituberculosis drug therapy. PAS is often included in such a regimen. I place great emphasis on the presence of calcified nodes in posterior mediastinum and the retroperitoneal regions of the abdomen. These could have been old calcified tuberculous lymph nodes which served as a source of the fatal miliary dissemination. Such calcified nodes are also found in histoplasmosis.

*Dr. Freedman**: Thank you, Dr. Siltzbach. The Menghini needle biopsy of

* Resident in Pathology, The Mount Sinai Hospital, New York, N.Y.



FIG. 2. Two conglomerate granulomas in the peripheral area of the liver. Several Langhan's giant cells are seen (arrow) (H & E $\times 100$).

the liver performed during life showed granulomatous lesions with giant cells of the Langhan's type, but without caseation (Fig 2). The bone marrow biopsy also contained tuberculoid lesions, with many histiocytes (Fig 3). Acid fast stains performed on all the tissues were negative. When the liver and bone marrow biopsies were examined under high power field, intracellular organisms were seen, suggesting a fungal disease. Although omitted in the protocol, the patient was treated with amphotericin in addition to isoniazid and para-aminosalicylic acid.

At autopsy she was deeply jaundiced and the abdomen was distended by ascites. The spleen weighed 1,500 grams (normal 150 grams), and was soft and mottled with hemorrhages. The abdominal lymph nodes were large and showed evidence of necrosis and calcification. The lymphoid follicles were reduced in size, and there was marked reticuloendothelial proliferation. Silver stains of the spleen demonstrated intracellular organisms (Fig. 4).

The liver was enlarged to about three times the normal size. The capsule was smooth, and the cut surface showed uniformly distributed areas of necrosis and fibrosis. There was a disarray of the liver architecture. Cords of necrotic liver tissue were disrupted by fibrous tubercles which showed peripheral Kupffer cell proliferation. Both Kupffer cells and dying hepatocytes were filled with oval-shaped organisms (Fig 5). In addition there was evidence of cholestasis.

The kidneys were slightly enlarged and showed a few petechial hemorrhages.

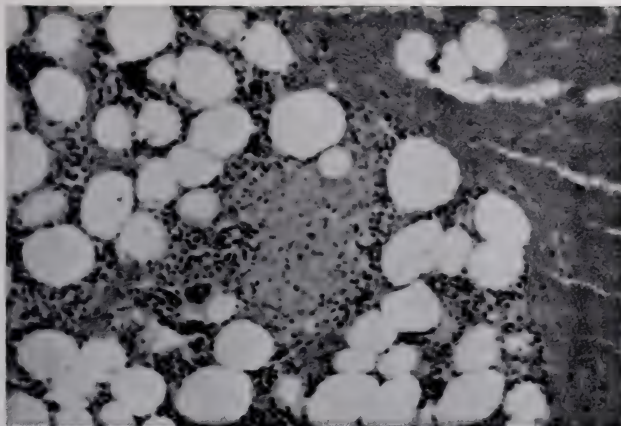


FIG. 3. Granuloma within the bone marrow (H & E $\times 200$).

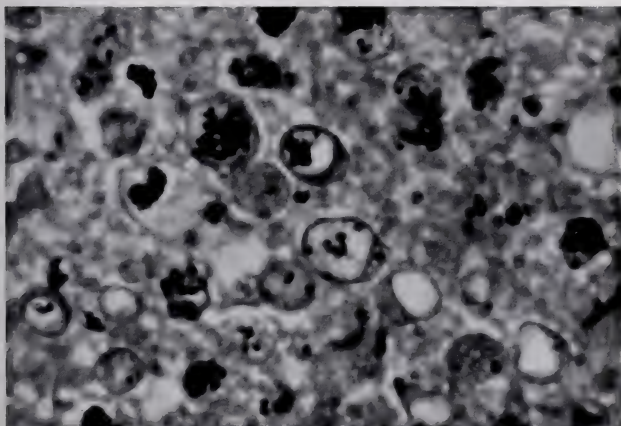


FIG. 4. Intracellular organism in the histiocytes within the spleen (Silver methenamine $\times 400$).

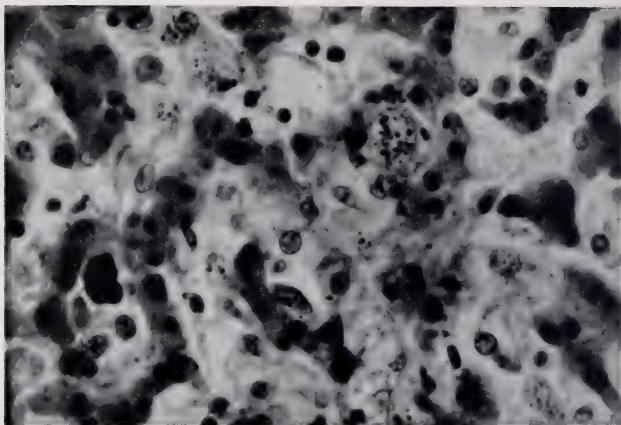


FIG. 5. Necrotic hepatocytes and Kupffer cells containing intracellular organisms (H & E $\times 400$).

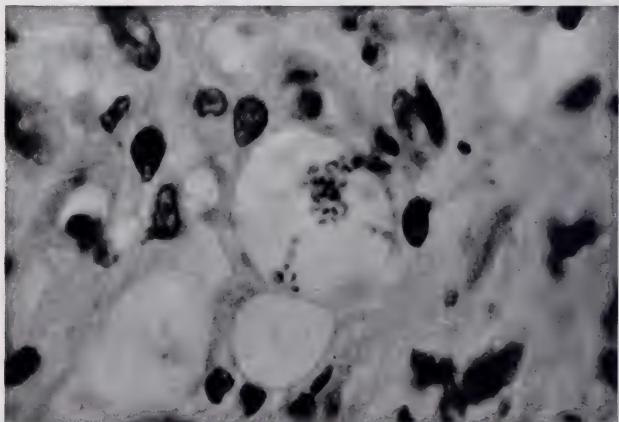


FIG. 6. Histoplasma organisms within the bone marrow (H & E $\times 960$).

The stomach and the remainder of the intestinal tract were unremarkable except for a few petechiae.

The lungs were voluminous and grayish white nodules were found on the subpleural surface. In the hilum were large calcified nodes. A subacute type of pneumonia was present, and within the exudate many histiocytic cells containing intracellular organisms.

The bone marrow was somewhat hypocellular, and contained abundant ovoid intracellular organisms that were identified by culture as *Histoplasma capsulatum* (Fig 6).

Dr. Siltzbach: How did the lungs appear microscopically?

Dr. Freedman: They were hemorrhagic but not productive and there was no caseation.

Dr. Siltzbach: This is very interesting because you'll recall I considered two conditions—tuberculosis and histoplasmosis before finally choosing tuberculosis. If the patient had come from the Ohio or Mississippi Valley, we would have chosen histoplasmosis rather than tuberculosis. I stressed that there is a difference between the calcification of lymph nodes in histoplasmosis and tuberculosis. In histoplasmosis, there is a tendency for the entire node to become calcified whereas in tuberculosis the calcification is lamellated or assumes a shape which I choose to call "popcorn" calcification. As you know, *Histoplasma capsulatum* is an organism that needs moisture and a temperate climate to grow so that it is common in the valleys around major rivers. Thus, in South America and in the United States, histoplasmosis is found around the Ohio, Missouri and Mississippi Valleys, and along the mouth and outlet of the Amazon.

Final Diagnosis: 1. SYSTEMIC HISTOPLASMOSIS INVOLVING LUNG, LIVER, BONE MARROW, LYMPH NODES AND SPLEEN.

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RADIOLOGICAL NOTES

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CASE NO. 299

A sixteen-year-old boy was admitted to the hospital with chief complaint of pain in the left ankle. Twenty-seven months prior to admission the boy sustained a trivial injury to the left ankle. A radiograph was obtained and reported as negative (Fig 1). Pain and swelling gradually subsided and the ankle became completely asymptomatic. Ten months prior to admission another minor injury was sustained while wrestling during school gymnastics. Four months prior to admission the ankle began to hurt during many of the usual gym activities. Pain persisted and gradually increased in severity until the time of admission.

Radiographic study of the left ankle was performed a few days prior to admission (Fig. 2A and B). There was a 5 cm ovoid lucent defect located posteriorly in the lower tibial metaphysis. There was no sclerosis or infiltration in the surrounding bone. The lesion was limited distally by the closed epiphyseal line. It caused a thin shell of the posterior cortex to bulge smoothly; the thinned cortical bone was deficient over the apex of the bulge where presumably the lesion was limited by periosteum. There was no indication of an infiltrating soft tissue mass. A zone of periosteal new bone was observed medially but no fracture was seen. Scrutiny of the radiographs made twenty-seven months previously revealed a minute defect in the subperiosteal cortex of the tibia at the site where the lesion was now located (Fig 1). The radiographic diagnosis was aneurysmal bone cyst.

At surgery the thin posterior cortical bulge was confirmed and the deficient bone over the apex of the lesion was also noted. A solid tumor was encountered, grayish-yellow in color, with fine spicules of bone within its substance. The tumor shelled out easily. The tumor bed was carefully curetted and an iliac bone graft was employed to fill the bony deficiency. The postoperative course was uneventful.

The pathologist reported a lobulated rubbery to firm tumor mass which on gross section was focally cystic and hemorrhagic, the small cysts measuring up to 6 mm in diameter. Histologically there were noted irregular vascular channels filled with red blood cells. There was an irregular scattering of multinucleated giant cells. Some areas were undergoing irregular and imperfect calcification. The histologic diagnosis was aneurysmal bone cyst.

DISCUSSION

The term aneurysmal bone cyst was used by Jaffe and Lichtenstein (1) in 1942 for a benign, solitary, lytic bone lesion, which was described originally

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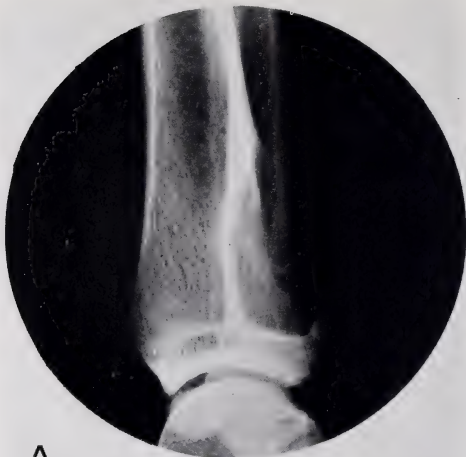


Case 299, Fig. 1. Lateral view of left lower leg and ankle taken twenty-seven months prior to admission shows a minute defect in the subperiosteal cortex of the distal tibial metaphysis posteriorly, measuring 4 mm in length and 1 mm in depth. It is located 2.5 cm above the epiphyseal line (arrow). No other bony abnormality is noted.

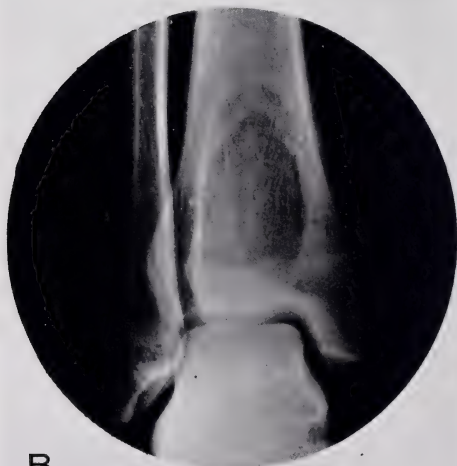
in 1893 by Van Arsdale (2). The lesion had been known previously by a spectrum of terms: ossifying hematoma, subperiosteal giant cell tumor, atypical giant cell tumor, benign angioma, and benign bone aneurysm. Although the etiology is not known, the lesion is most likely a dysplastic developmental bony abnormality (3).

Typically, the lesion is located eccentrically in the metaphysis of a long bone or in a vertebral appendage of a child or young adult. Its hallmark is the "blow-out" configuration (4). The lesion may occasionally appear in other bones (5, 6). The typical roentgen features as illustrated by the case presented may of course be absent (7), and in such cases the roentgen differential diagnosis may include giant cell tumor, unicameral bone cyst, non-ossifying fibroma and other "giant-cell variants," hyperparathyroidism and post-traumatic effect (8, 9). Malignancy is not ordinarily in question although aggressive local growth and recurrence may necessitate radical surgery to eradicate the lesion. Local excision and curettage, with bone chips employed to fill a large defect, will usually suffice for control (10).

It is generally accepted that aneurysmal bone cyst is subperiosteally ori-



A



B

Case 299, Figs. 2A and 2B.

ented in origin; this is inferred from its eccentric location and cortical expansion. It is of great interest in this case, therefore, to be able to document a tiny subperiosteal lesion before any deformity occurred (Fig 1), and to reflect on its rapid progress over a twenty-seven month span. Whether the history of trauma is significant is, of course, speculative.

—Harvey M. Peck

Case Report: ANEURYSMAL BONE CYST WITH DOCUMENTED SUBPERIOSTEAL ORIGIN.

Acknowledgment

This case is presented through the courtesy of Dr. Harold Grosselfinger, Good Samaritan Hospital, Suffern, New York.

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Case 299, Fig. 2A. Lateral view of left lower leg and ankle taken shortly before admission shows a large ovoid defect measuring 5 cm in length located posteriorly in the lower tibial metaphysis. There is no sclerosis or infiltration in the surrounding bone. The lesion is limited inferiorly by the closed epiphyseal line. A thin shell of cortex bulges smoothly over the lesion posteriorly but only periosteum is left over the apex of the bulge.

Case 299, Fig. 2B. Frontal view of ankle again shows the defect. The superior margin appears to be bevelled, due to the superimposition of anterior and posterior extensions of the lesion. The lower margin stops precisely at the closed epiphyseal line. There is periosteal new bone on the inner aspect of the lower tibial metaphysis but there is no indication of fracture.

CASE NO. 300

A two-year-old white female was admitted to the hospital because of an attack of bronchial asthma, at which time routine urinalysis had shown evidence of infection. Urine culture was strongly positive with growth of over a million colonies of *Escherichia coli* recorded. Despite three months of antibiotic therapy, repeat urine culture remained positive with growth of over one hundred thousand colonies of *E. coli* recorded. The patient was therefore readmitted to the hospital for urological evaluation.

General physical examination revealed no abnormality and routine laboratory studies were normal except for the urinary findings. Intravenous pyelogram was performed (Fig 1). There was good function bilaterally. The internal structures of the right upper tract were dilated and blunted, both ureters were dilated, and the right ureter was tortuous. There was 2.7 cm of renal parenchyma separating the top of the right kidney from the most superior internal collecting structure, greater distance than expected and greater than on the opposite side. In the bladder, delayed films demonstrated a 3.5 cm exquisitely sharp and round lucent filling defect which occupied the floor of the bladder just to the right of the midline. The diagnosis of a ureterocele was suggested. The configuration of the upper pole of the right kidney raised the question of a duplicated system with blockage and failure of function in the superior portion. A voiding cystourethrogram was performed. The patient appeared to void well, but a satisfactory demonstration of the urethra itself was not obtained.

The patient was explored and a large ureterocele was found in the floor of the bladder. A large opening was found in the base of the ureterocele measuring approximately 1 cm in diameter, apparently a ureteral orifice. This was catheterized for 5 or 6 cm. On the superior contour of the ureterocele there was another ureteral orifice of more normal caliber, but this could not be catheterized during surgery. The ureterocele was resected and the bladder closed with a suprapubic catheter left indwelling.

Postoperatively, the patient's urinary tract infection resolved on antibiotic therapy. Twelve days after surgery, a cystogram was performed (Fig 2). Sixty cubic centimeters of opaque material was introduced into the bladder via a straight catheter. The ureterocele was no longer seen. Marked reflux occurred into a very tortuous and dilated right ureter with retrograde filling of the collecting system of the upper pole on the right side. The refluxed opaque material delineated the entire duplication, and the internal structures were markedly dilated and blunted.

DISCUSSION

A ureterocele is a mass within the urinary bladder composed of prolapsed mucosa of the distal ureter. When the bladder is filled with opaque material from below, the ureterocele presents as a homogeneous negative shadow; it is filled with non-opacified urine and surrounded by contrast material. When



Case 300, Fig. 1. Sixty minute film from intravenous pyelogram shows a sharply outlined 3.5 cm round lucent filling defect occupying the floor of the bladder. There is dilatation of both ureters and tortuosity of the right ureter. The right upper tract is dilated and the internal structures are blunted. An arrow points to the top of the right kidney, the margin of which is 2.7 cm from the opaque material in the most superior internal collecting structure. The comparable distance on the opposite side is within normal limits. The presumption here is that there is a duplication of the collecting system on the right side with the superior portion of the system not visualized. The filling defect in the bladder suggests a ureterocele, ectopic in location, related to the orifice of the ureter draining the superior duplication.



Case 300, Fig. 2. Radiographs made after the introduction of 60 cc of opaque material into the bladder via a straight catheter reveal prompt reflux into a markedly dilated and tortuous right ureter, but this is a different ureter from that demonstrated on the intravenous study. Opaque material reaches the superior duplication which is dilated and blunted. The examination was performed twelve days after resection of the ectopic ureterocele.

both the lower ureter and the bladder are filled with opaque material, as during intravenous pyelography, both the outside and the inside of the ureterocele are delineated by contrast material and only the thin wall of prolapsed mucosa creates a negative shadow. With slight prolapse and a small lesion, this thin negative shadow assumes the characteristic "cobra-head" configuration. However when the lesion is large, as in the case presented, hydrodynamics cause it to become spherical.

The ureterocele generally obstructs the ureter from which it originates. When large, it may obstruct the ureters of both sides. It may be confused with a bladder neoplasm or may even prolapse through the urethra (1). There is an unusually frequent association with duplication of the urinary tracts, and as in the case presented, the ureterocele then derives from the ureter which drains the more superior renal pelvis and which inserts more inferiorly in the bladder floor (2).

—Harvey M. Peck

Case Report: URETEROCELE, DUPLEX COLLECTING SYSTEM, AND OBSTRUCTIVE UROPATHY.

Acknowledgment

This case is presented through the courtesy of Dr. William Bernstein and Dr. Marvin Buttermann, Good Samaritan Hospital, Suffern, New York.

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CASE NO. 301

A fifty-six year old woman consulted her physician with a chief complaint of weakness. For two or three weeks she had become progressively more tired and weak, epigastric pain had developed, and some weight loss was noted. A history of black stools was elicited. On examination, the patient was markedly pale and had epigastric tenderness. Laboratory data revealed hemoglobin 7.1 gm, red blood cells 2.8 million, and stool guaiac examination strongly positive. The patient was admitted to the hospital for further evaluation.

Past history revealed an episode of dizziness and epigastric pain lasting twenty-four hours which had occurred two years prior to admission. There was no history of rectal bleeding or black stools at that time. No laboratory tests were obtained. Gastrointestinal series was performed (Fig 1 a and b). No abnormality was noted at that time, but in retrospect there was a 2.5 cm. round filling defect which projected into the air shadow of the fundus on an erect view, and was seen en face on a prone film.

On admission to the hospital, physical examination revealed some epigastric



Case 301, Fig. 1A. Erect posteroanterior view of the stomach from a gastrointestinal series performed two years prior to admission shows a 2.5 cm soft tissue shadow projecting into the air bubble medially about at the level of the esophago-gastric junction. The barium-air fluid level is located just below this soft tissue shadow which is not coated by barium. Remainder of the stomach shows no unusual feature.

tenderness but there was no other positive finding. Gastrointestinal series was performed (Fig 2 a-d). A very large filling defect in the proximal stomach was noted with smooth margins and a large central ulceration. The radiologist advanced the diagnosis of a large sarcoma, probably a leiomyosarcoma.



Case 301, Fig. 1B. Prone drinking film in the right anterior oblique projection (reversed in reproduction) includes the esophagus and upper portion of the stomach. Barium runs around a smooth, sharply outlined, round filling defect in the fundus of the stomach (arrow). The defect is located slightly below and lateral to the esophago-gastric junction. The fact that it is rimmed by barium in the prone position suggests that it is on the anterior rather than the posterior wall. The roentgen features in this en face view are consistent with a submucosal tumor.

After transfusion therapy, the patient was explored. A large tumor of the fundus and cardia of the stomach was found; proximal gastrectomy was performed with esophagogastrostomy and pyloroplasty.

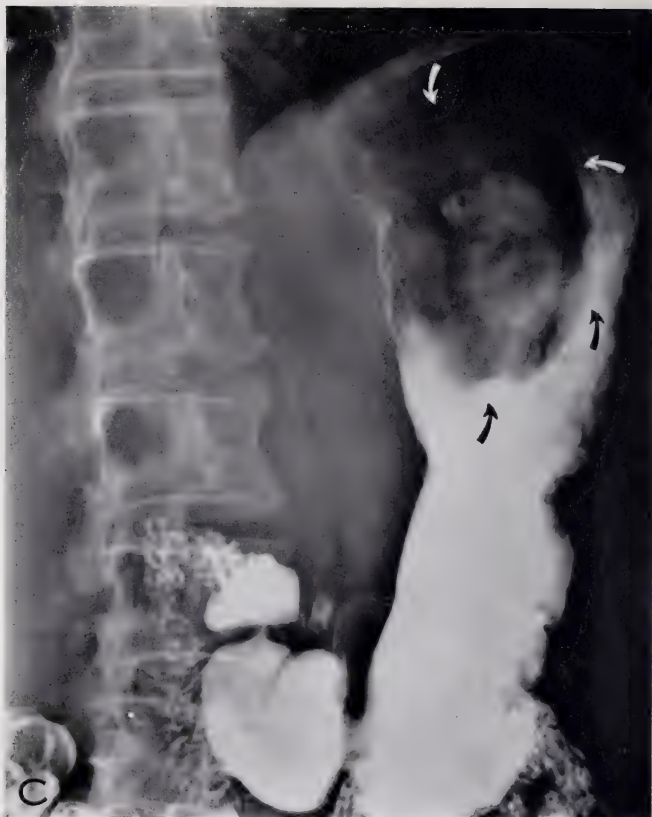
The pathologist described a large cauliflower-like tumor in the gastric speci-



Case 301, Fig. 2A. Prone posteroanterior view of the stomach from a gastrointestinal series performed at time of admission shows a very large filling defect occupying the upper portion of the body of the stomach. The lesion measures 8 cm in greatest diameter and the margins are quite smooth (*arrows*). Within the lesion there is seen a large amorphous collection of barium which represents ulceration. The dramatic change in size is noted in comparison with Fig. 1A.



Case 301, Fig. 2B. Prone drinking film of the esophagus in right anterior oblique projection includes the esophagus and the upper portion of the stomach. The filling defect is outlined by air superiorly and by barium inferiorly (arrows). Within the lesion the ulcer crater is filled by air and is recognized by a zone of increased lucency. Compare this illustration with Fig. 1B.



Case 301, Fig. 2C. Prone right anterior oblique view of the stomach shows an en face view of the large mass. The margins are smooth (arrows). The central ulceration is filled with barium.

men with a large central ulceration. The peripheral tumor margins were rolled and smooth without nodularity. The tumor completely replaced the muscularis and caused puckering of the underlying serosal tissue. Neither the surgeon nor the pathologist found any evidence of local spread and several lymph



Case 301, Fig. 2D. Erect posteroanterior view shows the stomach filled with barium with the fluid level reaching almost to the top of the lesion. Barium delineates the smooth lateral margin of the lesion (*along lateral arrows*). The upper margin of the soft tissue mass projects into the gastric air bubble (*arrow A*). Barium also outlines the irregular depths of the ulceration (*medial arrows*).

nodes which were examined were negative for tumor. Histologically, there were fascicles of neoplastic spindle cells with frequent mitotic figures and the histologic diagnosis was leiomyosarcoma.

DISCUSSION

The roentgen features in this case are typical. On the initial study the lesion presented as a submucosal mass. The surface pattern seemed smooth, the margins were exquisitely sharp, and the contour of the wall blended gradually with that of the mass. There was no ulcer or nodularity to suggest a malignant character. It is of more than little interest, therefore, to observe the remarkable transformation which occurred over a two year period. The lesion ultimately became quite large and bulky, and developed a saucer-like central ulceration with an irregular base. The symmetrical shape, smooth margins, absence of nodularity or evidence of surrounding infiltration are features which favor the diagnosis of sarcoma rather than carcinoma. Of course, once the submucosal nature of the lesion is recognized on the original study, carcinoma becomes an unlikely possibility. From the spectrum of sarcomata, leiomyosarcoma and lymphoma are the two most likely choices.

—Harvey M. Peck

Case Report: GASTRIC LEIOMYOSARCOMA WITH REMARKABLE PROGRESS OVER A TWO YEAR PERIOD.

Acknowledgment

This case is presented through the courtesy of Dr. Julius Cohen and Dr. Alfred Moscarella, Good Samaritan Hospital, Suffern, New York.

CASE NO. 302

A forty-three year old woman consulted her physician because of pain in the right ankle region for approximately eight months duration. She stated that the pain had come on gradually, there was always local tenderness, and occasionally there was some redness of the overlying tissues. She localized her pain precisely to the distal tibial shaft above the malleolar region. She denied chills, fever, or systemic illness, and there was no past history of an acute or unusual infection. Her family physician palpated a thickening of the bone of the lower tibial shaft and referred her for X-ray examination.

Conventional radiographic study of the right lower tibia showed an ill-defined lucent zone in the distal metaphysis with a thin surrounding sclerotic margin. It measured 2 cm in length, and was somewhat elongated in shape. A very minimal periosteal reaction was seen on the medial aspect of the tibia at the level of the lesion (Fig 1). Laminagraphic sections through the lesion were performed in frontal and lateral projections (Fig 2 a and b). The studies confirmed the presence of the lesion and a somewhat irregular sclerotic margina-



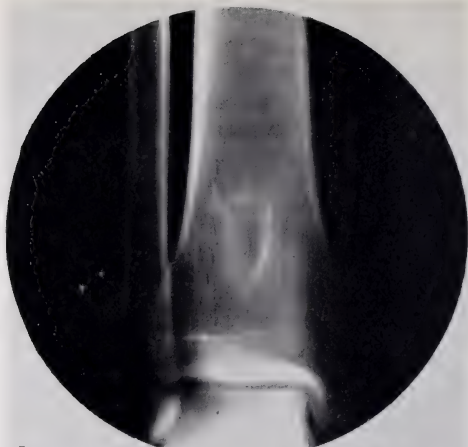
Case 302, Fig. 1. Internal oblique view of the right ankle demonstrates a 2 cm ill-defined lucent zone in the distal tibial metaphysis with a thin sclerotic margin. A very minimal periosteal reaction can be seen on the medial aspect of the bone at the level of the lesion.

tion. The lesion was oriented to the medullary cavity rather than the cortex. Periosteal new bone was again delineated.

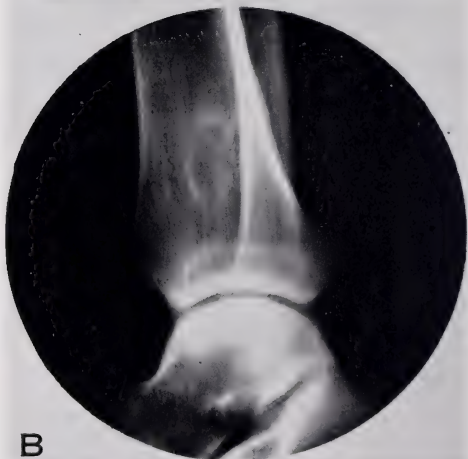
The patient was admitted to the hospital where general physical examination and routine laboratory data were normal. The right distal tibia was explored through an anterior approach. The surgeon confirmed the presence of periosteal new bone. In the medullary cavity, a small abscess was encountered which contained 2 to 3 cc of thick pus. No tumor or neoplasm was found. The tibia was saucerized and postoperatively, continuous through and through irrigation and suction with antibiotic therapy was employed.

The pathologist reported histologic evidence of infection with areas of acute and chronic inflammatory reaction and necrosis; there was no evidence of neoplasm. Cultures of the pus grew *Staphylococcus aureus*, coagulase positive.

The postoperative course was uneventful with gradual defervescence of a mild temperature elevation. Three months later there was no clinical evidence of infection, and the patient was ambulating normally with no pain.



A



B

Case 302, Fig. 2A. Frontal laminagraphic section through the lesion delineates the lucent defect and its thin sclerotic margin. The lesion is not perfectly symmetrical. It does not reach the cortex. The surrounding bone shows no unusual feature.

Case 302, Fig. 2B. Lateral laminagraphic section through the lesion reveals a more ovoid shape in this projection. Periosteal new bone is seen along the posterior margin of the tibia at the level of the lesion.

DISCUSSION

Chronic osteomyelitis often presents a distinctive complex of clinical and radiologic findings. In his book, Brailsford (1) recounts Sir Benjamin Brodie's clinical description of, and the author's own experience with, this condition which has become known as Brodie's abscess. Typically, the lesion occurs at the metaphyseal end of a long bone. The history is inordinately long and symptoms of pain often date back many months or many years. The bone is tender and may be thickened to palpation. Radiographically, the lesion is lytic and somewhat ill-defined with a sclerotic periphery. Long duration and increased severity result in better demarcation. The lesion is not round as a rule but rather elongated in shape; it is usually metaphyseal in location, rarely subperiosteal or in the mid-shaft. The process is generally limited by the epiphyseal line and does not involve the epiphysis or the joint. There is no sequestrum. Periosteal new-bone formation usually is seen and accounts for the clinical thickening of the bone, but may occasionally be absent. The pus is usually sterile on culture, but when cultures are positive the organisms are the same as those found in acute suppurative osteomyelitis (2).

Differential diagnosis includes various neoplastic and inflammatory conditions: Ewing's sarcoma, metastatic deposit, eosinophilic granuloma and non-specific granuloma, tuberculosis and other specific bony infectious processes.

—Harvey M. Peck

Case Report: CHRONIC OSTEOMYELITIS (BRODIE'S ABSCESS).

Acknowledgment

This case is presented through the courtesy of Dr. Julius Cohen and Dr. Harold Grosselfinger, Good Samaritan Hospital, Suffern, New York.

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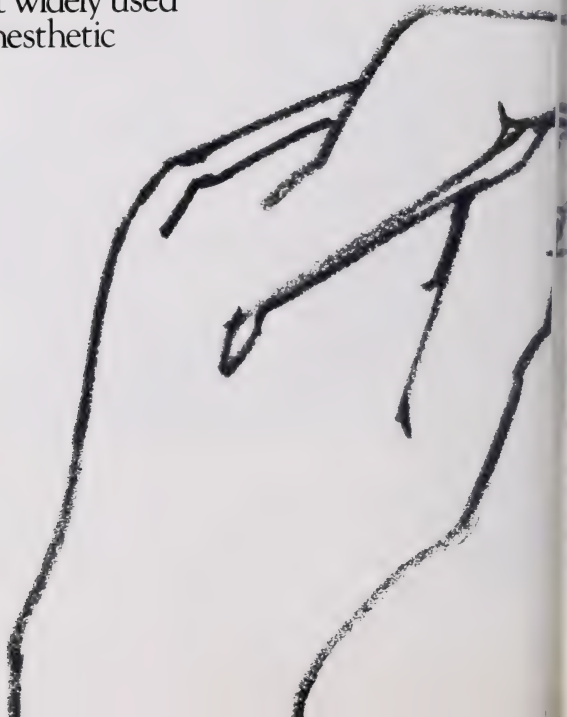
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In Memoriam

BELA SCHICK
1877-1967

On December 6, 1967 Dr. Bela Schick, world renowned scientist and humanitarian, died in his ninetieth year of an illness which lasted but a few weeks.

Bela Schick's parents, Jacob and Johanna Pichler Schick, lived in Graz, Austria, but Bela, second of four children, was born prematurely in Boglar, Hungary, on July 16, 1877 while his mother was visiting Dr. Telegdy, her uncle.

Bela studied medicine at the Karl Franz University in Graz, Austria, from 1895 to 1900. Bela Schick's diligence, perseverance, talent, and modesty attracted some of his teachers, Professors Friedrich Kraus, Meinhard Von Pfaundler, and Theodore Escherich, all of whom became interested in his future. His desire to become a pediatrician was answered when he became a volunteer in the Pediatric Department under Prof. Escherich. There he met Dr. Clemens Von Pirquet. A very close friendship and collaboration began which resulted in remarkable discoveries in the fields of infection and immunology. In 1902, Escherich became Director of Pediatrics at the University of Vienna and invited Von Pirquet and Schick to join him.

From the observations of the treatment of scarlet fever with the Moser serum came the appreciation of the incubation period, the accelerated reaction, and serum sickness. These observations led the way to the concept of "Allergy," a term coined by Von Pirquet in 1905, and the book "Serum Krankheit," authored by Von Pirquet and Schick. In 1906, Schick began his studies on diphtheria and in 1913 announced the epoch-making discovery, the skin test for diphtheria immunity. After Escherich's death in 1911, Von Pirquet was summoned to be Director of Pediatrics at the University of Vienna. Schick was invited to remain as Assistant. He later became Privat Dozent and in 1918 Prof. Extraordinarius. In 1923, he left Vienna to become Chief of the Department of Pediatrics at The Mount Sinai Hospital in New York and soon thereafter he also became Director of Pediatrics at Seaview Hospital for Childhood Tuberculosis. Upon retirement from Mount Sinai in 1942 he served as Director of Pediatrics at the Beth-El Hospital and later as Visiting Professor at the Albert Einstein Hospital. There, the Department of Pediatrics was named the "Bela Schick Department of Pediatrics," a tribute to a man of world renown.

Dr. Schick was the recipient of many other awards and honorary memberships in pediatric societies throughout the world. Among many others, the Addington (British) gold medal for "the most valuable discovery for relieving pain and suffering in humanity"; the New York Academy of Medicine gold medal presented to him in 1938 on the twenty-fifth anniversary of the discovery of the Schick test, and the John Howland award given to him by



BELA SCHICK, M.D.
1877-1967

the American Pediatric Society on May 3, 1958, pleased him greatly. The recognition which touched Bela Schick most was the album presented to him in 1933 by Dr. William H. Park in behalf of the Department of Health of New York City, signed by one million children who received the Schick test as part of a campaign to eliminate diphtheria from New York.

In the words of the Dean of American Pediatrics, Prof. E. A. Park, Emeritus Professor at Johns Hopkins School of Medicine, "Dr. Schick's greatest discovery was Catherine Fries to whom he was married on December 3, 1925." For forty-two years Catherine and Bela lived in harmony. They travelled often and widely. They enjoyed their many friendships here and in every part of the world. Catherine's devotion to her husband and his to Catherine were extraordinary and beautiful to the very last.

René J. Dubos, famous scientist and author, Professor at the Rockefeller Institute and friend of Bela Schick, wrote the preface to the book "Bela Schick and the World of Children." The first sentence reads: "To his countless friends throughout the world the hero of this book is known as a very lovable human being, endowed with much vigor, tempered by gentle smiling wisdom." Later he also wrote "To hundreds of millions of other men over the whole planet, the name Schick calls to mind not a person, but merely a scratch on the arm performed to test susceptibility to diphtheria. Like Volta, Pasteur and a few other scientists whose contributions affect our everyday life, Bela Schick must resign himself to seeing his name reduced—or is it not rather magnified—to the size of a common household word, one of almost universal usage."

In the epilogue of the same book, Prof. E. A. Park wrote "It is a pleasure to read about my great friend, Bela Schick whom I so wholly admire and when self-seeking bigoted, evil men keep our minds in turmoil and make us anxious and fearful for the future, it should be a relief to you to be led away for a little in the green pastures and still waters of his tranquil life." Later, "The reason that he is a great teacher is because his store of knowledge is so great and so unique. I believe that he shines most as a teacher of the privileged few because the gems of experience fall as the result of jostlings of chance rather than by intention and one has to be close in order to pick them up. In character he is so simple, open and friendly, so shy as almost to be called bashful and so good and kind that to become acquainted with him is to love him."

It was my good fortune to be associated with Dr. Schick from May 1925 through 1942 and to remain a close friend thereafter for the rest of his life. I was one of those privileged few who was close enough to Dr. Schick to be able to pick up the "gems of experience" dropped by him.

Professor Bela Schick leaves his widow, Catherine, and a sister, Lilly Schick, both of New York.

SAMUEL KARELITZ, M.D.
for the
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Crib Deaths: Their Possible Relationship to Post-Partum Depression and Infanticide

STUART S. ASCH, M.D.

It has been variously reported that between 20 and 30,000 infants are found dead in their cribs from unknown causes each year (1, 2). These mysterious and baffling deaths have all been placed in the descriptive category of "Crib Deaths" or "Sudden Unexpected Death (S.U.D.) in Infants." This category is now considered to be the leading cause of death in infants under one year, if the first two weeks of life are excluded (2, 3).

I suggest that there is good psychiatric reason to believe that a large proportion of these deaths are actual infanticides.

Many of these deaths of unknown etiology have several specific characteristics in common. The average age of the infant is usually two to three months (rarely more than 5 months); the infant is put to bed in good health but is found dead in the early hours of the morning, usually face down in the crib. One investigation reports that the highest incidence of the deaths occurs in January, with another peak in May (4). It is probably more frequent with boys. On autopsy, usually nothing is found as a cause of death.

Such a well-circumscribed and well-delineated clinical phenomenon certainly suggests a common etiology. A great deal of work has been done and is being done to find an etiological agent. Various hypotheses including accidental smothering with the blanket and an enlarged thymus, have been considered and ruled out. At present, most research in this area postulates infection with an unknown virus, or an anaphylactic reaction to some milk protein.

It is my hypothesis that the etiological "agent" must be sought in another direction and that a large part of these sudden unexpected deaths are infanticides, perpetrated by the mother as a specific manifestation of a post-partum depression.

This hypothesis is based on psychoanalytic data dealing with the dynamics of states of depression and has been developed from specific studies on the psychology of the post-partum state, including my own experience over many years as psychiatric consultant to the obstetrical department of The Mount Sinai Hospital of New York.

I have reported what I consider to be the universal fantasies and dynamics of the pregnant and post-partum woman (5).

A short period of depression, the "blue period," is most likely universal during the immediate post-partum period (6). This is readily understandable

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in psychoanalytic terms as a universal reaction to an emotionally significant loss. In this instance, it is the loss of the pregnancy state, and of the associated feelings and fantasies that surround a mental image of the fetus. During pregnancy the fetus is inevitably and normally invested with all kinds of special meanings and fantasies, both conscious and unconscious, including the acquisition of a phallus or the reunion with mother. Before delivery the baby is always experienced to some degree as part of the image of oneself. The post-partum blue period is then, in part, similar to the reaction that follows the loss of any part of the body. It is analogous to the depression seen so frequently in surgical patients postoperatively. Part of the self has been removed and lost.

On another level, the period of pregnancy inevitably stimulates memories and fantasies of old mother-child relationships. The parturient has fantasies of herself in *both* roles, the child (or infant) she was in the past, and the mother she is now. Both images do exist simultaneously, although one can be alternately more prominent than the other. The dissolution of this mother-child relationship with the delivery is once again an experience of loss, and specifically the emotionally charged loss of the mother-child unity. Such a "loss" at delivery revives feelings associated with earlier experiences of loss in the mother's childhood, when she was not mature enough to handle it.

In the normal post-partum patient this is a self-limiting reaction, essentially a mourning reaction. This is a necessary and normal period during which the person must deal with the loss of a loved one through some ego modification (this includes changes in the self-image, and further growth in various ego abilities). The mentally healthy mother is emotionally flexible and can readjust and quickly develop interest in her new-born. It is this new relationship with the real baby which helps her to deal with the feelings of a loss; the loss of both the fantasied baby of pregnancy (which is experienced quite differently from the real baby), plus the loss of the old mother-child relationship that existed in fantasy.

It may be that the woman who *does* adjust quickly to her "loss" at delivery, is able to do so because her *main* identification is with the mother, rather than with the infant. This would imply that her early separations from the mother were dealt with through the formation of stable identifications with her mother. The resultant ego modifications would then derive from the development of a stable object constancy. Such stable identifications, formed very early, may be the basis of a healthy response to delivery, a relatively conflict-free libidinization of the relationship to her new-born infant with rapid resolution of the "blue period."

Post-partum depressions and psychoses tend to develop in those women who have never been able to adequately deal with problems of loss and separation in the course of their maturation and development. These are women who frequently have difficulty in establishing a warm, meaningful relationship with their new babies. Lacking such a facility to relate well, emotionally, to new personalities, these mothers may continue to experience the infant as an out-

sider. This is specifically a difficulty in investing the baby, who has now moved outside their bodies, with many of the values and meanings with which they had enveloped the fetus inside. These new feelings and attitudes that develop around the newborn are not just an amalgam of old feelings about oneself as an infant with her mother. Although such personal historic feelings are necessarily a part of the new relationship, a healthy mother-child relationship must also include entirely new values, and a new object representation. Otherwise we find the same kind of problems that we are familiar with in the individual who shifts from an oedipal object to a new one through displacement of the drives alone, who has not achieved a corresponding modification in the representation of the object in his mind. In both instances the *psychic* representation of the object has not changed significantly, although the real object has. The typical post-partum depressed patient is unable to establish either kind of object relationship. She can neither relate to the baby as a new object, nor can she create a neurotic relationship by directly superimposing the old relationship she once had with *her* mother. Such women continue to feel a loss after delivery. They remain depressed, and may even progress to psychosis if the premorbid personality has been too fragile.

In these post-partum depressions, suicide becomes a very real problem and remains a danger for many months.

It may be useful to outline at this point, the usual psychodynamic conflicts that beset depressed patients in general. A great deal of aggression is mobilized in a depressed patient, as a direct reaction to the loss of the important object. Such anger is usually not clinically apparent, since it is not *overt* anger directed towards outside objects. Rather, the depressed patient characteristically handles his anger at the important loss by feeling that he *himself* is no good, or that *something* about himself is no good. It is in this context that desperate and unrealistic attempts may be made to change the situation and undo the loss. These are usually attempts to get rid of the bad part of the self in some symbolic or even literal way in order to be loved again.

In the treatment of depressions, or of unsuccessful suicides after delivery, it becomes clear that these suicides are primitive attempts to undo the birth process, to undo the physical separation from the fetus. Careful investigation has made it apparent that such suicides have the fantasied aim of reuniting the mother-child unit in some symbolic manner, although the patient is usually not aware of this. Jumping from a building or out the window can be understood as just such an attempt at symbolic reunion with mother on a primitive, infantile level. It seems to represent reentry through the portals into mother's body.

A related but distinct aim of the suicidal post-partum patient is the wish to destroy something she feels as a "bad" part of herself. Too often this feeling of a "bad part" is transposed onto the baby, especially if the baby is experienced as a foreign body, if the mother is unable to relate to it as a thing to be loved. It is at *this* point that the danger of actual harm to the infant arises.

This is one of the many situations in which we can see how suicide and

homicide are closely related, and often even alternative phenomena. They both represent alternative modes of aggressive acting out on a hated object, since the object may be experienced either inside the self as part of the depressed patient's self hate, or outside the self (7, 8).

This shifting of roles in the pregnant woman, the confusion and alteration of identities—who is the mother and who is the child—is a completely normal phenomenon. I would even consider such lability of identifications during pregnancy as necessary for a satisfactory pregnancy and later for nurturing.

However, this kind of alternation and confusion between child and mother can become a serious problem if the mother-child relationship in the pregnant woman's childhood and infancy was defective and had provoked a great deal of hostility that was inadequately dealt with at that time. Although hostile and even murderous fantasies directed towards the child are *not* at all unusual during pregnancy (in fact, they are probably the rule), they can present serious problems if there had been serious abnormality in the pregnant woman's early relationship with *her* mother.

"The primary conflict . . . (with both the fetus or newborn) concerns not the woman's relationship with her child, but the relationship with her own mother" (9).

A patient of mine went into a long-lasting depression following the birth of a daughter. She had great difficulty in controlling her rage at this child. The daughter had been given the patient's first name, Catherine, while her middle name was that of the patient's mother's, and finally her nickname was that of the beloved Godmother, "Kitty." My patient loved cats all her life and still kept a stuffed cat she had had as a baby.

When she became pregnant during her analysis, the intensity of her murderous rage increased, especially when fetal movements appeared in the fifth month. For some time there was a very real danger of her killing the child Kitty. It was clear from the material developed that the rage was being displaced from both her own mother whom she disliked but couldn't consciously hate, and the fetus. The material made it quite clear that there was a rapid shifting in identifications from among the three generations, Kitty and the fetus, the patient, and her mother. There were times when it was even difficult to know which of these was the *conscious* object of her rage.

This patient finally committed suicide, with a note explaining that she was protecting the unborn baby from a bad mother, clearly the internalized image of her *own* mother. This case has been reported previously in more detail (10).

A schizophrenic woman seen in consultation presented this confusion of identities between self and child/fetus even more directly. She had married immediately after her mother's death ten years before. She came for advice about her sixth "accidental" pregnancy over these ten years. "I'm still mourning for my mother," she stated, and then went on to ask to be aborted, because "I'm not ready for motherhood. I can't stand being a mother."

Throughout the pregnancy she felt her mother was a "Dybbuk" inside her.

She believed her voice became "mother's" at times and her image in the mirror "mother's" face.

When her children cry, she throws them into the back of the crib, "deep into it, against the far wall," she says, as if symbolically pushing them back into the womb. During the present pregnancy she picked up her cat and slammed it against the wall on several occasions. She was aware that this was connected with rage at the pregnancy. (I did not find out if the cat was or had just been pregnant.)

While the danger of suicide in post-partum depression is well known, the incidence of infanticide during this same period has almost *never* been commented on. The one important exception is a striking study conducted in England in 1927 (11). Hopwood reviewed the admissions to Broadmoor, the State Criminal Lunatic Asylum, for the period from 1900 to 1924. He found that 42.8% of all female hospitalizations were because of infanticide. Almost all these acts were committed within one year of childbirth. It was Hopwood's observation that post-partum psychosis, "...usually takes the form of melancholia with delusions of unworthiness, and in these cases ideas of suicide and homicide are more common." Of the total of 166 admissions for infanticide, 98 had suicidal ideation while 59 had made actual suicide attempts. These figures again indicate the close relationship of suicide and homicide (infanticide).

McIlroy commented on Hopwood's study adding his own observation, "the (post-partum reaction) patient has suicidal or homicidal tendencies, often on impulse. She may cut her throat or strangle or drown her infant" (12).

In 1924 the English Parliament passed a specific Infanticide Act that reduced the crime of infanticide during the post-partum period from murder to a felony (12). This act took official recognition of the fact that infanticide was often a specific expression of a psychopathological reaction to childbirth.

For some reason, neither this psychiatrically sophisticated piece of legislation, nor Hopwood's impressive statistics on the incidence of infanticide, seems to have been noticed by medical groups in this country. This is all the more striking since it is not unusual to pick up the paper and read of a woman who jumps from the roof either while holding her infant or after throwing the infant out first. I have called attention to the phenomena of infanticide and childbeating as manifestations of post-partum depression (5).

It is understandable that the idea that a mother might kill her own child is an abhorrent one, and that most people are really unable to tolerate such a thought. It seems quite possible that many instances of infanticide are camouflaged with an innocuous or accidental cause of death by a benevolent family physician. "The implication that parents were instrumental in causing injury to their child is often difficult for the physician to accept" (13). Overt cases of infanticide or even the verbalization of infanticidal thoughts by pregnant women or new mothers, (even though such thoughts are quite common) usually meet with repugnance and avoidance in the listener. We do not like to recognize the existence of brutality to infants, especially brutality from the

parents. This is why such an extensive phenomenon as the related "battered child" could have remained hidden so long (14). Only now, after the initial publicity about that syndrome, are we beginning to recognize its extent and the frighteningly high incidence of brutal aggression directed towards infants.

When this background of information dealing with postpartum depression and associated suicide-homicide impulses is kept in mind while examining the phenomenon of "crib deaths," the significant correlation becomes evident. "The murderous hostility against her child is the nodal point of the mother's depressive reaction" (15). "Crib deaths" *all* occur during the post-partum period and usually within the second to the third month. The infants are found face down. The most frequent cause of death in cases of discovered infanticide is asphyxia (16). The infants are put to bed in good health only to be found dead in the early morning hours. Clinically it is known that these same early morning hours correspond to the period of greatest agitation in depressed individuals. Another curious correlation that still requires further explanation is an apparent "seasonal" incidence, since "crib deaths" are higher in January and May (4). The provocative correlation is that the incidence of *suicide* in the whole population seems to be highest in December and January, and possibly in the spring again (although these figures need further confirmation) (17). Although autopsy usually fails to reveal any pathological change, (there *are* no physical changes with suffocation), one careful series revealed an unexpectedly high incidence (up to 5%), of fractured skulls (18).

It thus seems quite possible that a large percentage of "crib deaths" are actually infanticides occurring as part of a postpartum depression, unknown to or disguised by the family and/or the family physician.

These findings are presented as a preliminary report on the psychiatric aspects of "crib deaths." Further investigative work is now being carried out, including psychiatric evaluations of the families of all "crib deaths" in New York City, within 24 hours of their report.

Summary

The phenomenon of sudden unexplained death in infants or "crib deaths" are described.

The dynamics and phenomology of post-partum depression is also described; and the relationship of suicide to homicide is emphasized.

The hypothesis is presented that a large proportion of the annual 20,000 to 30,000 "crib deaths" in the United States are covert infanticides, manifestations of a post-partum depression in the mother.

As a result of confusion in identities between mother and fetus/baby, in the pregnant or post-partum woman, infanticide may occur in place of suicide.

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The History of Carotid Artery Ligation

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Although ligatures were known to Celsus (25 B.C.–A.D. 50), there is no record of carotid ligation in antiquity or medieval times. Ambrose Pare (1510–1590) reintroduced ligatures to renaissance surgery but there is no report of a successful carotid artery ligation until the early nineteenth century.

David Fleming, a young and relatively inexperienced British Naval Surgeon, while serving on H.M.S. *Touant*, was the first to successfully ligate the carotid artery in the neck. From the incomplete naval records available, the following information is known. On October 9, 1803 Mark Jackson, a servant on board the *Touant* cut his throat in a suicide attempt. Fleming treated him immediately, and convalescence was satisfactory until October 17th when, during a coughing spell, the carotid artery burst and “torrents of blood issued from mouth and nose.” Fleming tried to secure the vessel through the wound but owing to its friable condition this attempt failed. Although Fleming had never heard of such an operation, he cut down on the carotid artery below the wound and tied a ligature around it. Jackson survived and made an uninterrupted recovery.

Prior to this successful result other ligations of the cervical carotid artery had been done. However, until Fleming’s case there is no record of a survival.

Abernathy (1764–1831), one of John Hunter’s famous pupils in London, ligated the common carotid artery for hemorrhage in 1798. However, his patient died about thirty hours later.

During the first half of the nineteenth century, ligation of the carotid artery was done frequently not only for hemorrhage and peripheral aneurysms but also for epilepsy, psychoses and trigeminal neuralgia.

William MacGill (1802–1833), of Maryland was the first American surgeon to ligate both common carotid arteries (1823).

There are many reports concerning ligation of the cervical carotid arteries in cancer of the head and neck. The first authentic report in which ligation of the common carotid artery became necessary during the removal of a neck tumor is that of Cogswell of Hartford, Connecticut on November 4, 1803. The patient made a good postoperative recovery but died of hemorrhage on the 20th day.

Benjamin Travers of London ligated the common carotid artery in a patient with an arteriovenous fistula and pulsating exophthalmos on May 23, 1809; the patient recovered.

Valentine Mott (1785–1865) of Long Island, a great pioneer in vascular

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surgery ligated the carotid for aneurysm in 1829 and both carotids simultaneously in 1833. All in all, Mott has a record of 51 common carotid artery ligations and two internal carotid ligations.

Norris (1847) of Philadelphia collected 149 cases of carotid ligation. Fifty-four patients died as a result of the operation. In 25, severe cerebral symptoms developed within three days, and later in seven more. Thirteen died of cerebral involvement.

Guthrie (1862) stressed the dangers of carotid ligation reporting cerebral symptoms in 47 of 213 cases.

In 1868 Pilz collected 600 cases of ligature of the common carotid artery with a mortality of 43%.

Zimmerman (1892) collected 6 cases of ligation of the common carotid artery; mortality 31%, cerebral symptoms 26%.

In 1902, Horsley ligated the right common carotid artery in the neck for an intracranial aneurysm discovered during a craniotomy for a suspected brain tumor. His patient was observed for five years and remained in good health.

Referring to carotid artery ligation Matas (1909) stated that "the possible occurrence of cerebral disturbance has invested a simple technical procedure with a gravity associated with but few operations."

Halstead in 1914 advocated the use of metal bands for partially occluding the carotid arteries and thus avoiding the serious risk of complete ligation.

Homans (1920) was one of the first observers to stress the importance of degree of shock and blood pressure in determining the occurrence of complications due to carotid artery ligation.

Freeman (1921) discussed the causes of cerebral disturbances following carotid ligation. He believed ischemia with cerebral softening followed ligation when the circle of Willis did not provide an adequate collateral circulation. He mentioned Zimmerman's theory which stated that cerebral complications resulted from emboli which broke off from a thrombus at the site of ligation.

Locke (1924) reviewed 588 cases of arteriovenous fistula between the internal carotid artery and the cavernous sinus. Thirty-eight were treated by ligation of the internal carotid artery in the neck. Twenty-one per cent were cured, seventy per cent improved, nine per cent died.

In 1927, Egas Moniz described cerebral angiography and cases of intracranial aneurysms so discovered were reported by many workers in this field.

Nattrash (1928) reported one of the earliest cases of an intracranial aneurysm diagnosed on clinical grounds for which ligation of the internal carotid artery in the neck was done.

Harvey Cushing (1932) said, "I have ligated the internal carotid many times without apparent symptoms. I don't now recall any accidents, but there may have been some. I have been careful to restrict these ligations to young or middle-aged persons without vascular disease."

The efficacy of the circle of Willis in maintaining an adequate circulation following occlusions of one of the internal or common carotid arteries remains as a matter of much controversy, this in spite of greatly increased clinical ex-

perience and carefully conducted experimental studies. Because of significant anatomical differences in the circle of Willis it is hazardous to apply the results of ligation of the major feeding vessels in animals to man.

Dandy (1933) stated that after the age of 35, total ligation of the internal carotid artery is dangerous.

After studying many reports Pitcher and Thuss (1934) concluded that ligation of the common carotid artery will be followed by cerebral symptoms in 20 to 30% with permanent residual damage in some cases, and rarely, death. They were unable to provide criteria on which to base a preoperative prognosis and admonished: "The common (or internal) carotid artery should therefore be occluded only in cases in which a greater danger lies in permitting it to remain unoccluded."

Dorrance (1934) discussed the immediate and late complications of carotid artery ligation. Among the immediate complications he described fainting, headache, hemiplegia, aphasia and death. During the next seven to ten days signs of severe cerebral disturbance may develop. He advanced the following theories:

1. Anemia due to failure of circulation because of anomalies of circle.
2. Thrombosis and embolism.
3. Ischemia due to vasoconstriction.
4. Circulatory stasis.
5. Intracerebral hemorrhage.

Concerning ligation of large arteries generally Reid (1934) gave the following advice:

1. Avoid fine ligatures which may cut through arterial walls.
2. Partially occluding and crushing ligatures are dangerous.
3. Absorbable ligatures may disintegrate unevenly.
4. Intimal surfaces brought in contact cannot unite.
5. It is safer to doubly ligate and cut between than to ligate in continuity.
6. Less damage is done to the vessel wall if it is temporarily occluded proximally and distally while drawing the ligature tight.
7. The size of the ligature should vary with the size of the artery.

Watson and Silverstone (1939) reported twenty common carotid ligations during an 11 year period on an active head and neck tumor service (Memorial Hospital, New York City). Eleven patients died within five days of operation. Nine patients survived. However, of these two died within three months. In one, death was due to an infected thrombus from the ligated artery. In three fatal cases where the brain was examined at autopsy, edema, softening or other gross cerebral changes were noted. Unfortunately, careful neuropathologic study of the material was not carried out. Age did not seem to be a significant factor in prognosis in this series.

In 1940, Schorstein was able to describe sixty cases of carotid ligation for intracranial aneurysm. Twenty-seven had been reported previously. The remaining 33 were contributed by members of the Society of British Neurological Surgeons.

Rogers (1945) advised double ligation and section of a large artery in preference to ligation in continuity. Division permits the ends to retract and become securely closed. Also, vasospasm is suppressed, embolism from the site of ligature is less likely to occur, nor is such a vessel likely to ulcerate and bleed later on.

Rogers (1947) discussed the function of the circle of Willis in relation to ligation of the carotid arteries. In his Arris and Gale lecture to the Royal College of Surgeons he reviewed the history of ligatures. The first account of the use of ligatures is given by Celsus who lived from 25-30 B.C. to 45-50 A.D. Celsus favored double ligation with section of the vessel between the ligatures. Mr. Lancelot Haire (1786) was the first to advocate cutting the ends of ligatures close to the knot.

Rogers points out that ligating an artery is not merely a matter of sealing off a pipeline. The artery must be regarded as a living distensible, tubular structure possessing elasticity, irritability, contractility and the power of retraction; characteristics which depend on a neuromuscular mechanism with widespread connections throughout the vascular system. Interference with this mechanism often may have far-reaching results.

The advantages of double ligation with division between overligation in continuity are:

1. It is complete. Recanalization cannot take place after the absorption or loosening of the ligature.
2. Sectioning the artery severs the accompanying sympathetics in the adventitia and thus abolishes peripheral vasospasm which the ligature may induce.
3. If the ligature should slip or in some other manner become undone or ulceration take place at its site, fatal hemorrhage is less likely to occur than from an opening in an artery ligated in continuity. It is well known that death due to hemorrhage may occur when an injury produces a hole in a major vessel, whereas, if a large artery is torn apart due to injury, the ends retract and when the blood pressure falls hemorrhage stops.
4. The retraction of the divided ends of a large artery reduces the liability of subsequent embolism from the ligature site. Also the pumping action when the vessel is tied in continuity is obviated.

Rogers summarized the steps to be taken to mitigate the effects on the peripheral circulation of ligation of a major artery.

1. Divide the artery.
2. If possible place the proximal ligature distal to a large branch thus avoiding a blind end and allowing the full force of the arterial pressure to be directed to the branch and not to the blind pocket of the main artery.
3. Keep the blood pressure at its previous level.

Rogers reported twelve cases of carotid artery ligation mostly for intracranial aneurysm without complications. He believed that intracranial complications were frequent following internal carotid artery ligation. He believed

that ligation of the internal carotid raises the pressure in the carotid sinus with reflex lowering of the systolic blood pressure, whereas common carotid ligation lowers the pressure in the carotid sinus and avoids reflex circulatory disturbances.

Sweet and Bennett (1948) reported the results of intra-arterial pressure studies following occlusion of the various vessels in the neck. When the internal carotid was occluded, the systolic blood pressure distal to the occlusion was reduced to 50 per cent of the original while the pulse pressure fell to 25 per cent of the original.

They found that significant retrograde flow from external to internal carotid did not occur when the common carotid artery was occluded. In fact, reverse flow from internal to external was equally likely to occur.

Selverstone (1950) described his method for gradual occlusion of the carotid vessels. He devised an ingenious clamp having an external portion which protruded through the incision. The circulation through the carotid can be regulated in a matter of seconds. The external portion can be detached leaving the occluding clamp in the wound.

Experiences with the Selverstone clamp have been variable. In some cases it has proved very satisfactory. On the other hand, the clamp carries with it all the disadvantages of a large foreign body, an open wound and an irritating element in contact with sensitive nervous structures.

McConnell, Sanigan and Gladhill (1952) performed 14 ligations for saccular aneurysms. Three patients died and one had hemiplegia. In 15 patients treated by craniotomy there were no deaths and two hemiplegias.

Johnson (1953) confirmed Sweet and Bennett's observations in 11 patients with aneurysms of the circle of Willis.

Geoffrey Jefferson (1953) described his plan. He usually ligates the common carotid artery first. In 68 ligations in two years, 50 were without complication or mortality. When hemiplegia develops, Jefferson felt it was due to failure of circulation in the perforating vessels of the internal capsule.

Wolfe (1953) (Cardiff Royal Infirmary) advised:

1. Immediate ligation and division of common carotid artery in patients with:
 - a. Second bleeding.
 - b. Patients remaining stuporous.
 - c. Past history of previous hemorrhage.

Poppen (1956) described a modification of the Blalock clamp which he believed had certain advantages over other methods of carotid occlusion. He advocated applying the clamp to the internal carotid artery in patients with aneurysms which arise from the intracranial carotid or its bifurcation. Local anesthesia is used. An oblique adequate incision is made. A site free of atherosclerotic plaques is chosen. The clamp is applied and closed. In poor risk patients the artery is only partially occluded. Strips of muscle are prepared from the sternomastoid muscle. Wire ligatures are threaded through the muscle strips setting them to act as cushions. Ligatures are laid in position around

the internal carotid arteries proximal and distal to the clamp. Wires are twisted so that the loops conform to the original caliber of the artery and produce no constriction. A third ligature of heavy silk is placed around the artery close to the clamp. The wound is closed bringing out the ends of the wire and silk and leaving the head of the clamp and its calibrations fully exposed. At the bedside, the patient is *never* left alone. Pulse and blood pressure are recorded every 20 minutes. Frequent neurological check-ups are made and an intravenous drip kept running. If patient does not tolerate complete occlusion, very gradual closing is done over 5 to 6 days. If occlusion is well tolerated, the wound is reopened and the muscle covered wire ligatures are tightened fully; the distal one first, the clamp is removed and the silk tied.

In December of 1965, J. R. Gibbs described a new technique for closure of the carotid artery in the neck. His method employs an ingenious device for causing torsion of the internal or common carotid artery. It has the advantage of producing complete closure of the vessel, while permitting rapid restoration of the circulation if hemiplegia or other untoward signs develop.

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The Temporomandibular Joints: A Survey of Disorders and Treatment Methods

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Introduction

For many of the past thirty years, the study of disorders of the temporomandibular joints has been greatly influenced by the theories of Costen, an otolaryngologist. In 1934, he described a symptom complex that came to be known as Costen's syndrome (1). The symptoms he described included loss of hearing, tinnitus, pain in the ears and temporomandibular joints, and vertigo. He believed the symptoms were due to posterior and/or superior displacement of the mandibular condyle caused by the loss and wear of posterior teeth and the resulting overclosure of the mandible. Therefore, Costen suggested a treatment based primarily on the restoration of the dentition. As late as 1955 he said that "restoration of balanced occlusion usually removes the source of stress and damage (to the temporomandibular joint) so that pain and trismus are relieved. Fortunately, this type constitutes the largest fraction of the cases." Although the practice of "opening the bite" (2) is still widespread, several authorities, particularly Sicher, (3) question not only the treatment but also the entire explanation of Costen's syndrome. Restoration of the dentition is often costly, time-consuming, and most important, irreversible.

In 1937, Schultz published a report on the treatment of painful clicking and subluxation of the temporomandibular joint with intraarticular injections of sodium psyllate, a sclerosing solution (4). Although Schultz's treatment is painful and ineffective, his views that the mandibular condyle should not move anterior to the articular eminence of the temporal bone gained wide acceptance.

Thus, the study of causes of disorders of the temporomandibular joint was dominated by two essentially geometric concepts; (1) overclosure of the mandible (vertical) and (2) anterior movement of the mandible (horizontal).

In 1959, Schwartz published his book on the temporomandibular joints (5). Two of his views are of particular interest. The first is that the temporomandibular joints are susceptible to the same disorders to which other joints are susceptible. These disorders are only modified because of the presence of teeth. Schwartz's second view is that the musculature, not the teeth, is the source of many of the functional joint disorders.

Disorders

All attempts to classify temporomandibular-joint disorders seem artificial, perhaps because several of these disorders may exist at the same time and at

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the same site. Nonetheless, some classificatory system such as the following is necessary:

Congenital Abnormalities

Many cases of congenital abnormalities involving the temporomandibular joints and mandible are found in the literature. The cases primarily involve hyperplasia, hypoplasia, or aplasia of the mandible and temporal bones (6).

Traumatic Disorders

Condylar fractures are most often associated with a history of recent trauma, pain, and swelling about the temporomandibular joints. Mandibular movements are usually restricted, and deviation to the affected side is common. Radiographic examination is essential. Children suffering from the so-called "Battered-Child Syndrome" should always be examined for condylar fracture.

Cervical traction, common in the treatment of whiplash injury, may be injurious to the muscles of mastication. By forcing the teeth closed there may occur an increase in tonus that becomes intolerably painful. This can be demonstrated merely by clenching one's teeth for a few moments (8).

Infections

Infection of the temporomandibular joints is rare. It is most commonly introduced through penetrating wounds or during intraarticular injections (9). Rarely it is associated with syphilis, gonorrhea, tuberculosis, or measles (10). Infections of the middle ear, paranasal sinuses, and the salivary glands, particularly the parotid gland, are sometimes mistaken for temporomandibular joint disorders.

Neoplasms

Neoplasms involving the temporomandibular joints are not common. Osteomas of the condylar head are difficult to diagnose. Their growth is slow and the patient is often symptom free until there is interference with mandibular movements (11).

Rheumatic Disease

Degenerative joint disease occurs mostly in older people (12). In the temporomandibular joint as in other joints, the disease is often unilateral with crepitus and restricted movements. Sometimes there is pain in the affected joint. Radiographs may reveal spur formation.

As we all know, rheumatoid arthritis is a general systemic disease (13). When it affects the temporomandibular joints, there may be destruction of the mandibular condyle and glenoid fossa. This destruction is usually bilateral, though the extent may vary from one side to the other. Flexion contracture of the muscles of mastication may occur. Because of the destruction

on the bony components and the flexion deformity there may be a shift of the mandible and a resulting malocclusion of the teeth.

The temporomandibular-joint pain-dysfunction syndrome (14) is one of a class of muscle syndromes called myofascial pain syndromes (15). In fact, many disorders of the temporomandibular joints are not, in the strictest sense, joint disorders but are disorders of the muscles of mastication. As in other muscle groups, these disorders are characterized by pain that is usually associated with palpable "trigger zones." Accompanying this pain and arising in response to it, is mandibular dysfunction, usually restriction. Sometimes an audible clicking is produced during incoordinated mandibular movements. Other symptoms of disorder of the muscles of mastication include stiffness, muscle weakness, and spasm, which is involuntary sustained contraction.

Emotional Disorders

The stomatognathic system, like all organ systems, has associated with it disorders that are essentially psychogenic. These disorders range from the nearly pure types such as hysterical trismus (16) and the distorted body image of the schizophrenic to the results upon muscle tonus of emotions. Stress is often the cause of the temporomandibular joint pain-dysfunction syndrome (17).

Treatment

The usual methods of treatment employed in temporomandibular-joint disorders include the pharmacological, physical, surgical, dental and psychological.

Pharmacological Treatment

Muscle relaxants appear to have little effect on the muscles of mastication. Analgesics are effective in the control of pain associated with rheumatoid arthritis and degenerative joint disease. They are also helpful in controlling myofascial pain. Local anesthetics injected into so-called "trigger zones" afford dramatic but short-lived relief. Topical ethyl chloride sprays provide similar relief with the additional advantage that the patient can apply it himself. Steroids administered intraarticularly give relief in selected cases. Treatment with nonsteroid anti-inflammatory drugs, particularly indomethacin, has proved successful, and has further decreased the need for intraarticular steroid therapy. Ataractic drugs help decrease unconscious muscle activities such as clenching of the jaws and grinding of the teeth that may aggravate muscle spasm (9, 18, 19).

Physical Treatment

The methods currently used in physical medicine lend themselves well to the treatment of disorders of the temporomandibular joints. The most successful methods are:

- 1) Exercise—Exercise has almost universal application in these disorders.

It is the most reliable method of returning muscles in spasm to normal function. Exercise minimizes contracture and flexion deformity (20).

2) Heat—Moist heat applied to the affected part prior to exercise improves muscle tonus (21).

3) Prosthetic appliances—Appliances are of two general types. In one, the primary function is to change the relationship between the mandibular condyle and the glenoid fossa. The other type changes the relationship between the maxillary and the mandibular teeth (22). A discussion of these appliances is beyond the scope of this paper.

Surgical Treatment

Ankylosis—bony or fibrous, partial or complete—can only be remedied by surgery. Currently, a great deal of attention is being paid to techniques that afford the best immediate result and diminish the likelihood of future ankylosis.

Meniscectomy, or removal of the fibrocartilagenous disc, has been used widely in an attempt to alleviate all types of temporomandibular-joint pain and dysfunction. Meniscectomy seems best indicated for the alleviation of chronic, painful clicking in the temporomandibular joints. This operation should only be attempted after nonsurgical methods have failed (23).

Closed reduction of condylar fractures should be attempted whenever possible. Open reduction, although routinely practiced, may result in serious complications. The most important one is interference with normal growth of the mandible in the immature individual (7).

Neoplasms, primarily osteomas, require surgical removal.

Dental Treatment

Adjustment of the natural dentition has always been a popular method of treatment. Costen advanced the idea of increasing the vertical dimension of the teeth by prosthetic means. The numerous methods that have been proposed lend credence to the view that the value of dental treatment is not yet well understood. An evaluation of dental treatment is beyond the scope of this article. However, it should be added that complex and subtle complications, including noxious stimulation of the proprioceptive-nerve endings contained in the periodontal ligaments, may result from such treatment. It is possible to exceed the physiologic limits and adaptive capacities of the individual. Thus, great care must be used in the selection of patients for and in the execution of dental treatment.

Psychological Treatment

Any treatment has its psychological components. The success or failure of the treatment may hinge on the degree to which the dentist or physician understands and utilizes these components. Certainly, the oral cavity and its contents is an area of great emotional importance for many persons seeking help.

In addition, some patients complaining of face pain exhibit emotional problems that seem to supercede in importance the supposedly organic disorders for which the patients seek treatment. These patients should be referred to a psychiatrist for consultation.

Summary

The disorders of the temporomandibular joints are similar to the disorders associated with the other joints of the body. Their causes include trauma, infection, neoplasia, congenital abnormalities, rheumatic disease and emotional disorders. These disorders are modified by the anatomy and physiology of the particular joints. In the case of the temporomandibular joints an important factor is that the articulating components contain teeth.

Treatment consists of surgical, pharmacological, physical, dental and psychological methods.

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Early Results with 20 Femoro-Popliteal Vein Bypass Grafts for Severe Peripheral Ischemia

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Vascular reconstruction in the treatment of peripheral arterial insufficiency is accepted as an integral part of surgical therapy. The insertion of the patient's own, reversed, long saphenous vein as a femoro-popliteal by-pass has the widest application, and the greatest success for long-term patency (1-7).

This is a brief account of twenty such operations performed on consecutive suitable patients at this hospital during 1965. The indications for reconstructive surgery were gangrene or severe rest pain (Table I) in an attempt to avoid amputation. All patients had a femoral arteriogram or lumbar aortogram performed. Operation was carried out provided the popliteal, or anterior or

TABLE I
Clinical Details of 20 Treated Patients

Case #	Initials	Age	Diabetes	Complaint	Result
1	P.P.	68	Yes	Gang. toe	Patent graft
2	M.K.	78	No	Gang. toe	Patent graft—Dead
3	C.M.	49	Yes	Gang. toes	Patent graft
4	E.G.	72	Yes	Rest pain	Patent graft
5	A.F.	70	Yes	Gang. toes & foot	Patent graft
6	C.F.	83	Yes	Rest pain	Patent graft
7	A.C.	80	No	Gang. toes	Clotted graft
8	F.B.	72	Yes	Gang. toes & foot	Clotted graft—B/K amputation
9	S.D.	74	Yes	Gang. toes	Clotted graft—A/K amputation
10	S.L.	61	Yes	Gang. toes	Patent graft
11	M.P.	57	Yes	Gang. toes	Patent graft—B/K amputation
12	M.M.	75	Yes	Gang. toe	Patent graft
13	W.R. (amputee)	74	No	Rest pain	Patent graft
14	M.S.	79	Yes	Gang. toes & foot	Patent graft—B/K amputation
15	H.N. (amputee)	57	Yes	Gang. toe	Patent graft
16	A.M. (amputee)	54	Yes	Gang. toe	Patent graft
17	T.L.	59	Yes	Gang. toes	Patent graft—B/K amputation
18	T.O. (amputee)	63	Yes	Rest pain	Patent graft
19	S.R.	68	Yes	Gang. toe	Patent graft
20	T.D.	69	Yes	Gang. toes & foot	Patent graft—B/K amputation—Dead

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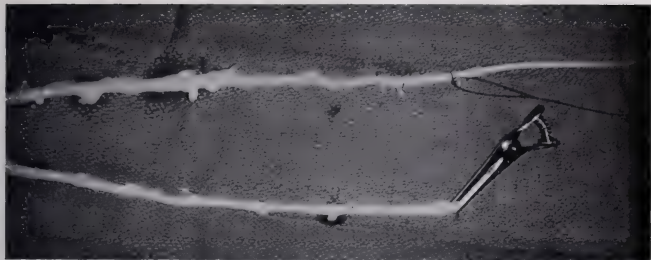


FIG. 1. Long saphenous vein just prior to insertion as by-pass graft.



FIG. 2. Large atheromatous plaque removed from common femoral artery before fashioning anastomosis.

posterior tibial artery was visualized. Only those patients whose arteriogram demonstrated neither an anterior nor posterior tibial artery in the upper or middle third of the calf were rejected for reconstruction, and treated with an above knee, or occasionally below knee amputation. Age and general condition were not accepted as contraindications to surgery, if the patient had been



Fig. 3. Femoro-popliteal artery occlusion, with lower portion of popliteal artery satisfactory for anastomosis. Run-off essentially through collaterals only.

active and ambulatory prior to the onset of gangrene or ischemic pain, and provided no knee contracture was present. Seventeen patients in this group had diabetes mellitus.

Technique

The standard operative procedure was used, as described in the literature (2, 3, 4, 6). Several technical points are of special importance. The operation was always carried out by two teams, each consisting of an attending surgeon and one resident. This shortened the operation time considerably. Unless the excised saphenous vein was unusually large, it was gently stretched over a Number 10, and then a Number 12 curved urethral sound. After this procedure it was distended with heparinized saline, ligation of all branches was confirmed, and the vein was maintained in this condition until its insertion into the leg. This maneuver produces a graft of almost uniform calibre (Fig. 1). We are aware of the suggestion by Taylor *et al* (8) that this

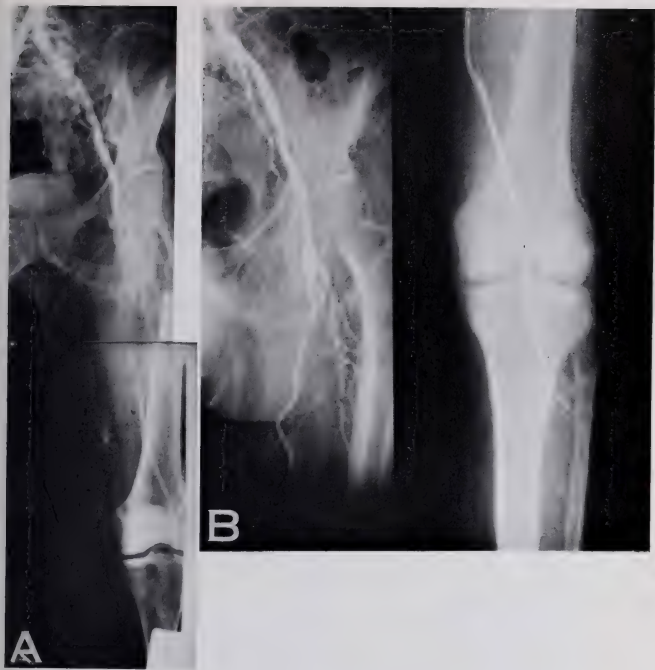


FIG. 4A. Long femoral artery occlusion, with poor run-off.

FIG. 4B. Somewhat redundant, functioning vein graft of good calibre one year after surgery.

temporary storage in heparinized saline may be a disadvantage because of its possible effect of separating the phospholipid portion of the protein molecules in the media. We have continued to use it awaiting further evidence regarding its detrimental effect. Prior to closing the extensive skin incisions necessary for exposure of the arteries and the long saphenous vein, we have trimmed off a thin layer of subcutaneous fat. This has resulted in a great reduction in the incidence of superficial wound complications.

Local endarterectomy has often been performed at the upper anastomosis, which is usually fashioned opposite the origin of the profunda femoris artery (Fig. 2). At the lower anastomosis we have avoided the addition of an endarterectomy, and have relied on shaping the vein graft in such a manner



FIG. 5A. Ischemic foot with gangrenous toe. Arteriogram showed femoro-popliteal artery occlusion.

FIG. 5B. Primary healing two weeks after toe amputation, and five weeks after successful femoro-popliteal vein by-pass graft.

that it also acts as a patch graft, thereby widening the lumen of the artery. The host artery at this level was either the popliteal, or the posterior or anterior tibial artery in that order of frequency.

Discussion

The graft was considered patent if, at the time of discharge from hospital, at least two different observers agreed that pulsation was felt in the graft behind the knee, or ankle pulses were present. The table summarizes the results of surgery.

Patency of the vein graft at the time of discharge from hospital will continue for long periods of time, leading to continued functioning of the graft in 75 to 85% of such patients over a five year follow-up period (2-5, 7). Our immediate patency rate of 17 in 20 patients is satisfactory, particularly in view of the poor state of the calf circulation as shown by most of the arteriograms (Figs. 3-4B), and the advanced degree of ischemia (Figs. 5-6B). Despite technical success, below-knee amputation became necessary in four patients (Case nos. 11, 14, 17, 20), as the local gangrenous process was very advanced. We feel that the patent graft was instrumental in ensuring rapid healing of the below-knee stump, and three of these patients are now fitted with a prosthesis and retain their own knee joint.

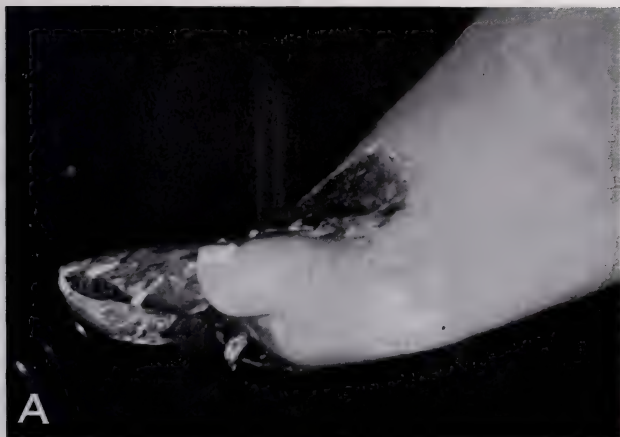


FIG. 6A. Gangrene of toes and forefoot. Arteriogram showed femoro-popliteal artery occlusion.

FIG. 6B. Complete healing six weeks after transmetatarsal amputation, and ten weeks after successful femoropopliteal vein by-pass graft.

The two deaths are acceptable in that the reported hospital mortality for amputation alone is 15-29% (9-12), and presents a similar challenge to the surgeon. Brief clinical details of these two patients are given.

CASE #2

Female, age 78, not diabetic, successful femoro-popliteal by-pass for gangrenous toes. Found dead in bed 2 days' postoperatively. Autopsy showed myocardial infarct.

CASE #20

Male, age 69, diabetic. Successful femoro-popliteal by-pass graft for gangrenous toes and foot, followed within 10 days by transtatarsal amputation to remove all gangrenous tissue. Three weeks later hemiplegia developed. As the remaining portion of the foot failed to heal, below-knee amputation was performed. The patient died 3 weeks later with hemiplegia and pneumonia.

The local condition was not made worse in any of the three surgical failures. Patient #9 had continuous rest pain and gangrene preoperatively, for which he required above-knee amputation one month after surgery. Patient #8 had gangrene of toes and the dorsum of her foot, for which below knee amputation was performed three weeks after the failed by-pass graft. Her stump healed slowly. Patient #7 still has an ischemic ulcer on her foot where the gangrenous toes were removed after the failed reconstruction. She is able to walk, but it is extremely painful.

Patients #13, 15, 16 and 18 were prior amputees on the other side, and were operated upon as they had become unable to walk with their prosthesis because of pain in the remaining leg. As all four patients have made excellent progress in their rehabilitation with no restriction due to the treated extremity, we feel the risk of carrying out surgery on a remaining ischemic limb is justified.

Summary

Twenty consecutive patients with gangrene or severe rest pain of a lower extremity are presented. A femoro-popliteal vein by-pass graft was performed on all patients, and was patent at the time of discharge from hospital or death in seventeen. Thirteen of these patients retained their ischemic extremity, whereas in the remaining four, in spite of a patent graft, below-knee amputation had to be performed. Four of the patients were prior amputees, and have been able to resume walking following successful vascular reconstruction in the remaining lower limb.

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Metastatic Infiltration of the Thyroid Gland Causing Hypothyroidism

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Metastasis of carcinoma to the thyroid gland is not uncommon. At post-mortem examination it has been found to occur in from 4 to 12 percent of cases (1-4). Despite this relatively high incidence of involvement of the thyroid with metastatic cancer, hypothyroidism resulting from such metastases is extremely rare. The case report presented here is a probable example of this unusual phenomenon.

Case Report

A 58 year old white woman was admitted to The Mount Sinai Hospital in September, 1966, for evaluation of hoarseness, progressive weakness and confusion. She had been well until October, 1962, when a left radical mastectomy was performed at another hospital. The pathologic diagnosis was scirrhous carcinoma of the breast. One lymph node contained metastatic cells. During the subsequent months she received a 5200 rad course of radiotherapy to the left chest wall and axilla in 26 doses. She did well until January 1966, when swelling and tenderness developed in the anterior neck. A protein-bound iodine done at this time was 7.3 $\mu\text{g} \%$.

In April 1966, she was seen in the thyroid clinic of The Mount Sinai Hospital. The thyroid was diffusely enlarged and firm, and had a granular texture with no discrete nodules palpable. The gland was not tender. The patient was clinically euthyroid. The protein-bound iodine was 7.3 $\mu\text{g} \%$ and the 24 hour radioactive iodine uptake by the thyroid gland was 7%. A tentative diagnosis of resolving thyroiditis was made. The patient was next seen in August 1966, because of progressive hoarseness, thick speech and difficulty in swallowing. She denied other symptoms of hypothyroidism. Vital signs were normal. The skin was warm and dry and the hair was coarse. The thyroid was enlarged, firm and nontender with a firm, pea-sized nodule palpable in the lower pole of the right lobe.

In September 1966, periorbital edema developed. The patient's pulse was 80 and regular. Her blood pressure was 120/90 and temperature 98.6 F. The thyroid was unchanged, but firm lymph nodes were palpable in the right supraclavicular fossa and the left anterior cervical chain. Indirect laryngoscopy showed paralysis of the left vocal cord. The lower third of the right hemithorax was dull to percussion and had decreased breath sounds. There was generalized muscle weakness and slow mentation. The protein-bound iodine was 1.8 $\mu\text{g} \%$, and the T-3 resin uptake was 0.67 (normal 0.8-1.3). The patient was admitted to The Mount Sinai Hospital for further evaluation.

The hemoglobin was 11.4 gm %; the white blood cell and differential count were normal. Erythrocyte sedimentation rate was 62 mm/hour. Urinalysis was normal. Blood chemistries, including liver function studies, calcium and phosphorus were within normal limits. An electrocardiogram showed low voltage in all leads. Chest x-ray revealed fluid at the base of the right lung and in the right interlobar fissure. Thoracentesis yielded 220

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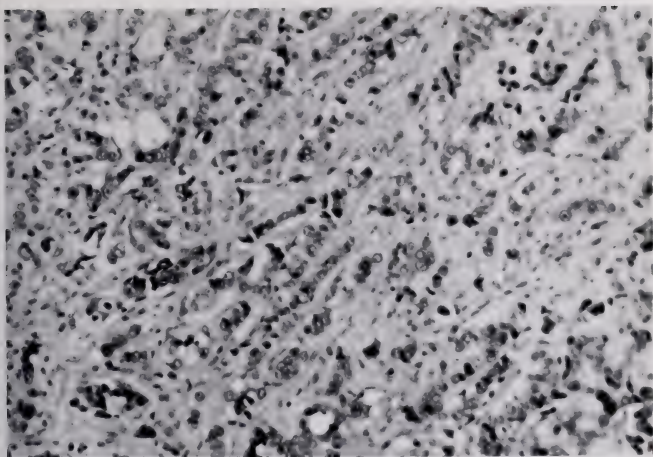


Fig. 1. Section of open biopsy of thyroid isthmus showing complete replacement of thyroid tissue by metastatic carcinoma. Hematoxylin and eosin, magnification 80 \times .

cc of slightly turbid yellow fluid with a specific gravity of 1.016, protein 2.52 gm %, and sugar 115 mg %. Cytologic studies showed no malignant cells. Post-thoracentesis chest x-ray showed no mass or infiltrate. Radioactive iodine uptake after three days of thyrotropin stimulation (10 units per day, Armour Thytropar) was 4.4%. Electroencephalogram, brain scan, cerebral angiogram and pneumoencephalogram indicated the presence of a posteromedial mass in the left frontal lobe of the cerebral cortex. Open biopsy of the thyroid isthmus showed metastatic carcinoma consistent with breast origin (Fig. 1). No thyroid tissue was recognizable in the biopsy specimen. Two lymph nodes from the right lower jugular chain also showed similar metastatic carcinoma.

The patient's course was one of rapid deterioration. She was treated with cytomel, prednisone, thiotepea and methotrexate and died on the 46th hospital day. Permission for post-mortem examination was not obtained.

Discussion

The necropsy studies of Willis (1), Rice (2), Hull (3) and Mortensen (4), have demonstrated embolic tumor cells in 4 to 12% of thyroid glands in patients dying of nonthyroidal malignancies. Metastatic carcinoma to the thyroid appearing as a goiter is much less common (5). Hypothyroidism resulting from neoplasms metastatic to the thyroid gland is even more rare, with only four such cases (Table I) reported in the literature to date. In 1931, Willis noted clinical hypothyroidism in a woman whose thyroid gland underwent metastasis from carcinoma of the breast (6). A similar case was reported by Winkler in 1932, in which serial studies of basal metabolic rate confirmed the develop-

TABLE I
Reported Cases of Metastatic Infiltration of the Thyroid Gland Causing Hypothyroidism

Author	Sex	Age	Site of primary	Time elapsed between diagnosis and onset of hypothyroidism	Hypothyroidism confirmed by
Willis (1931)	F	56	Breast	?	Clinical
Winkler (1932)	F	44	Breast	3	Clinical, Serial BMR
Sklaroff (1954)	F	73	Rectum	7	RAI uptake, Clinical
Shimaoka (1962)	F	44	Breast	5	Clinical, RAI uptake
Present case	F	58	Breast	4	Clinical, RAI uptake, PBI, T-3 uptake, T-4

ment of hypothyroidism (7). In 1954, Sklaroff described a woman whose thyroid gland was invaded by metastatic tumor seven years after a rectal carcinoma had been removed (8). In this case, the diagnosis of hypothyroidism was supported by a reduced radioactive iodine uptake. In 1962, Shimaoka *et al* found metastasis to the thyroid gland from a breast carcinoma causing clinical hypothyroidism documented by a low radioactive iodine uptake (9). Our patient had unequivocal hypothyroidism, and biopsy proved metastases in the thyroid gland. Without direct gross and microscopic confirmation at autopsy, we can only speculate that this patient's severe hypothyroidism was a result of metastatic carcinomatous replacement of the thyroid gland. The clinical evidence and the operative and biopsy findings, however, strongly suggest this thesis.

It is of interest that all five patients with hypothyroidism caused by thyroidal metastasis were females, and that in four of the five patients the site of the primary carcinoma was the breast. The time elapsed between diagnosis of the primary and the development of clinical hypothyroidism ranged from 3 to 7 years (Table I).

Acknowledgment

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Psychotherapeutic Drugs—Patterns of Use

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Introduction

Since the introduction of the Rauwolfia alkaloids and phenothiazines into medicine in the early 1950's, the role of psychotherapeutic drugs in psychiatry has become firmly established. There are few, if any, treatment facilities or treatment programs which do not seriously consider when and/or how to use these medications along with other treatment methods. However, despite this widespread use and intensive research interest, many questions remain. It is to be expected that fourteen years is not sufficient time in which to achieve a full or significant understanding of what these drugs do to and for the mind and behavior. The systems are too complex. But we might reasonably expect, after almost a decade and a half of use, that within the limits of the available data, there would be some consistent pattern to their use.

It is well known that drugs which affect the mind can, in themselves, influence behavior in a symptomatic way, often making it difficult to distinguish the symptoms of the illness from those possibly resulting from the drugs (1, 2). A clear knowledge of these effects would be a necessary requisite to the controlled use of the medications. To this end we undertook a "psychotherapeutic drug survey" to see if "behavioral toxicities" such as depersonalization, hallucinations, or non-organic confusion due to drugs contributed to the need for hospitalization.

The data for the first 44 admissions revealed no such contributing behavioral effects. In fact, there were very few side and toxic effects of any kind reported. Our observations did indicate that, while psychotherapeutic drugs were prescribed extensively by both psychiatrists and non-psychiatric physicians, there was no consistent pattern to the use of these drugs in terms of indications, dose schedules, duration of treatment, or care of the patient during the period of drug-taking (3, 4). The study was then continued with our interest focused on general patterns of drug prescription and use.

Method

Data were gathered on the patterns of psychotherapeutic drug use of psychiatric patients prior to hospitalization. A total of 152 consecutive admissions to The Mount Sinai Hospital Institute of Psychiatry were investigated. The first 44 were in pilot study; the remaining 108 were added as a general study of patterns of psychotherapeutic drug use.

All patients were interviewed as soon as possible after admission to the hospital by one of the investigators (J.M.P.); this was within 48 hours of admission. In addition to the information available during the course of the

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usual type of psychiatric interview, specific data concerning medication were obtained, using a standardized set of questions prepared for this survey designed to obtain as much data as possible about medication and the way in which it was prescribed.

Following the personal interview, a review of the current hospital record supplied additional information, helped to verify the history obtained from the patient, and permitted a comparison of the clinical evaluations made by investigators and the hospital psychiatrists.

Results

Diagnosis

There was close agreement between the investigators and the hospital staff in the evaluation of the patient in terms of presenting symptoms, mental status and diagnostic impression (Table I).

The most frequent diagnosis was schizophrenic reaction; this was made on the basis of the total clinical picture. The most frequent immediate reasons for hospitalization, however, were depression, anxiety and inability to function in customary environment (Fig. 1).

Major Symptoms Leading To Hospitalization

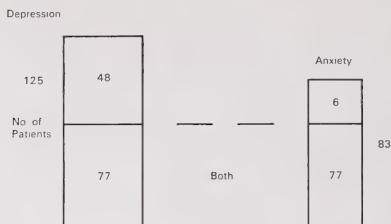
The usual current recommendations are that medications be prescribed according to the target-symptom model rather than the diagnostic classification (5-7). We therefore examined the drugs prescribed in relation to the outstanding symptoms leading to hospitalization. None of our patients had a simple symptomatic picture. The two most frequent symptoms were depression and anxiety (with or without psychotic behavior) and they often occurred simultaneously.

Depression was by far the most frequent symptom, occurring as one of the most disabling factors in 125 of the 152 patients or 82% (7, 8). Forty-eight of these severely depressed patients had no appreciable anxiety. Eighty-three patients (54%) showed severe anxiety with or without agitation; of these, 77 were also severely depressed. There were six patients only with severe anxiety and no depression (Fig. 1).

To emphasize further how frequent and severe the symptoms of depression were, we found that in our second sample of 108, 20 patients (19%) were

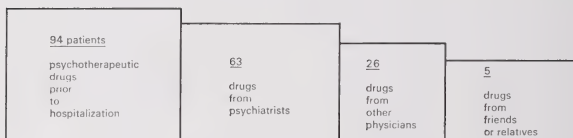
TABLE I

Diagnosis	No. Pts.
Schizophrenic Reaction.....	107
Manic Depressive Psychosis.....	3
Psychotic Depression.....	14
Psychoneurotic Reaction.....	23
Addiction.....	5



Note: not to scale.

FIG. 1. Most frequent symptoms.



Note: not to scale.

FIG. 2. Source of medication.

admitted to the hospital because of a suicidal attempt, and another 29 (27%) were admitted with suicidal ideas or wishes. Thus a total of 49 patients were so depressed that the danger of suicide contributed directly to their hospitalization.

Medication Prior to Hospitalization

There are many limitations in obtaining medication records from patients. Twenty-five patients in the second series of 108 had some difficulty in giving the exact name and dose of their medication. More patients had difficulty with the dose than with the name of their medication; however, only ten patients could not identify their medication.

Source of Medication

Of the 152 patients, 94 (62%) were treated with some psychotherapeutic drug in the 3 months prior to hospitalization. Of these 94, in 63 (67%) it was prescribed by a psychiatrist; in 26 (28%) it was prescribed by a non-psychiatric physician. Five patients (5%) received their drugs from relatives or friends (Fig. 2).

Types of Medication

An attempt was made to understand the reasons for the selection of any particular drug, the dose range and schedule. This was very difficult. There

was a lack of uniformity and consistency in drug or drug-combination choice, dosage, or duration of drug treatment in relationship to the symptomatology or the clinical picture. The following examples will illustrate this:

Case I. The patient was a 53 year old man. In November, 1964, he was hospitalized for severe depression. Prior to that hospitalization he was being treated privately by a psychiatrist with prochlorperazine* 5 mg *tid*. At the hospital he was treated with trifluoperazine dihydrochloride† 5 mg *tid* and amitriptyline hydrochloride‡ 50 mg *tid*. He improved. His medication was reduced to trifluoperazine dihydrochloride 2 mg *tid* and amitriptyline hydrochloride 25 mg *tid*. He was discharged on these doses of drugs to his private psychiatrist. After two months the depression returned; he became anxious and expressed somatic complaints. No attempt was made to increase his drug dosage although he had been helped by higher doses while in the hospital. He was readmitted, severely depressed and suicidal.

Case II. A 22 year old young woman was admitted after attempted suicide. On admission she was severely depressed and frightened. She had been having auditory hallucinations and frequent episodes of depersonalization, and had been treated by a psychiatrist for several months. Depression had been severe for at least two months. For one month she received chlorpromazine hydrochloride§ 25 mg *qid*; on the day of her suicide attempt, imipramine hydrochloride|| was prescribed 25 mg *tid*.

Case III. A 29 year old married woman had been treated by the same psychiatrist for nine months prior to admission. She was admitted in a state of manic excitement which had developed over a period of several weeks. Although the patient had been helped by thioridazine hydrochloride¶ during previous episodes, she received no medication prior to this hospitalization.

Combinations of Drugs

These appeared to be haphazard. Most patients received combinations of drugs. Sixty-four patients received several drugs simultaneously. There were some patients taking five or more drugs at the same time.

Case IV. A 17 year old girl was admitted because of attempted suicide. She had been treated by a psychiatrist for one and one-half years prior to hospitalization. On admission she was depressed, anxious, phobic and experienced frequent episodes of depersonalization. Her medication on admission was: 1) isocarboxazid** 10 mg *bid*; and 2) dextro-amphetamine†† 10 mg *bid* to improve her mood; 3) chlorthalidopoxide‡‡ 10 mg *bid* to calm her anxiety; 4) phenmetrazine hydrochloride§§ 25 mg *bid* to curb her appetite and help keep her weight down. (All were prescribed by her psychiatrist.); 5) secobarbital sodium||| 100 mg H.S. was prescribed by her family doctor. In addition, she smoked marijuana and took other barbituates and amphetamines with her friends.

* Compazine (Smith Kline and French).

† Stelazine (Smith Kline and French).

‡ Elavil (Merek, Sharp and Dohme).

§ Thorazine (Smith, Kline and French).

|| Tofranil (Geigy).

¶ Mellaril (Sandoz).

** Marplan (Roche).

†† Dexedrine (Smith, Kline and French).

‡‡ Librium (Roche).

§§ Preludin (Geigy).

||| Seconal (Lilly).

Patients with similar clinical problems were treated with completely different drug-combinations. Often patients were taking more than one drug of the same group at the same time, *e.g.*, more than one type of tranquilizer or more than one drug to elevate mood, such as an antidepressant and amphetamine.

Case V. An unmarried 28 year old woman with a severe depression had paranoid and somatic delusions, a thought disorder, and a flat and inappropriate affect. She had received her medication from an internist and was being treated simultaneously with imipramine hydrochloride 25 mg *qid*, chlordiazepoxide hydrochloride 25 mg *qid*, promazine* H.S., chlorpromazine hydrochloride 150 mg *tid*.

Case VI. A 24 year old female under treatment by a psychiatrist was admitted to the hospital because she threatened suicide. She had auditory hallucinations and paranoid delusions. Her medication prior to hospitalization was chlorpromazine hydrochloride spansule 150 mg *tid* and trifluoperazine dihydrochloride 2 mg *qid* with no change in the dosage as her symptoms became more severe. Two weeks prior to hospitalization, as her depression became very severe, one spansule of dextro-amphetamine was added daily.

Case VII. A 14 year old girl was admitted to the hospital because of attempted suicide. On admission she was very depressed. Although she was thin, she had the delusion that she was fat and was interested only in eating and dieting. She was in treatment with a psychiatrist for several months. He prescribed no medication, but recommended hospitalization. The patient had a severe crying spell and her mother took her to a hospital. The doctor there gave her chlordiazepoxide hydrochloride 10 mg *tid*, with which she made the suicidal attempt.

Case VIII. A 15 year old girl was being treated by a psychiatrist for five years prior to hospitalization. She was admitted because of attempted suicide. On admission her symptoms were severe depression, with anxiety and agitation, frequent episodes of depersonalization and somatic delusions. She, too, was a thin girl, with a delusional belief that she was obese. Medication prior to hospitalization was chlordiazepoxide hydrochloride 30 mg daily for many months, diethylpropion hydrochloride† one capsule daily from her family doctor, and chlorpromazine hydrochloride spansule 75 mg daily for several weeks prior to hospitalization.

Choice of Medication

Although depression with or without agitation was by far the most frequent symptom, tranquilizers, not antidepressants, were the most commonly prescribed medications. Often tranquilizers were the only drug used in severely and acutely depressed patients (Fig. 3). Compare with Fig. 1 showing main symptoms.

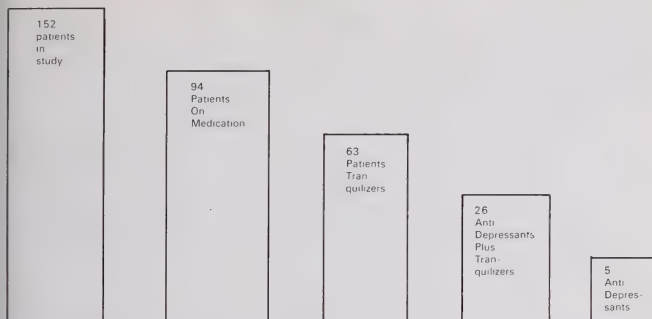
Case IX. The patient was a 50 year old housewife admitted from the emergency room because she threatened to commit suicide. On admission, her symptoms were severe depression with agitation, phobias, and severe and progressive incapacitating vomiting. Her psychiatrist treated her with meprobamate‡ 1200 mg a day and chloral hydrate 0.5 Gm *qid*.

Case X. The patient, a 56 year old man, was admitted because of a severe depression. He

* Sparine (Wyeth).

† Tenuate (Merrill).

‡ Miltown (Wallace).



Note: not to scale.

FIG. 3

could not work, withdrew from all social contacts, had insomnia, loss of appetite and constipation. As his mood became more depressed his intake of alcohol went up. His psychiatrist treated him with chlordiazepoxide hydrochloride 10 mg *pm*.

Case XI. A 21 year old female was hospitalized for the first time. For six months prior to admission she had become more depressed and anxious, had many somatic complaints and experienced frequent episodes of depersonalization. She saw her physician because of insomnia; he gave her sleeping pills (sodium pentobarbital*) with which she attempted suicide.

Choice of Tranquilizer Medication

When tranquilizers were prescribed there was often no relationship between the patient's symptoms and the choice of drug in terms of "minor" or "major" tranquilizer†, psychotic patients with severe secondary symptoms were often treated with "minor" tranquilizers.

Case XII. A 20 year old male college student was treated by a psychiatrist for two years continuously since his last discharge from the hospital. For the eight months prior to hospitalization his medication was trifluoperazine dihydrochloride and dextro-amphetamine 10 mg/day. His depression became deeper, with suicidal ideas. He was very anxious and frequently had feelings of depersonalization and unreality. The psychiatrist substituted diazepam‡ 5 mg *tid* and then, as the patient's symptoms continued to progress, he increased this to 5 mg five times a day. The patient suffered delusions and auditory hallucinations and heard voices telling him he was immortal. To prove it he stood in the path of a car. The medication as noted was continued up to hospitalization.

Case XIII. A 38 year old woman underwent her second post-partum psychosis. She was depressed, anxious, agitated, with an elaborate delusional system about her own destiny

* Nembutal Sodium (Abbott).

† "Minor"—nonphenothiazines usually recommended for neurotic anxiety. "Major"—phenothiazines usually recommended for psychotic anxiety.

‡ Valium (Roche).

TABLE II

Chlorpromazine Hydrochloride.....	100-400 mg
Trifluoperazine Hydrochloride.....	4-6 mg
Imipramine Hydrochloride.....	75-100 mg
Amitriptyline Hydrochloride.....	50-75 mg

and that of her child. A psychiatrist prescribed chlordiazepoxide hydrochloride 10 mg *tid* and when that did not bring relief he changed to chloral hydrate 0.5 Gm *qid*.

Case XIV. The patient was a 36 year old woman. Shortly before admission she became severely psychotic with auditory hallucinations in which voices were commanding her to do violent and frightening things. The family doctor prescribed chlordiazepoxide hydrochloride 10 mg *tid*.

Dose of Medication

Our data indicate that dosage schedules were usually below the recommended level and rarely did they reach the accepted therapeutically effective dosage (9, 10). The commonest daily doses for the most frequently prescribed medications are given in Table II. Although these may be adequate dose levels for patients who have achieved a state of equilibrium or whose symptoms are improving, these are doses which can have little if any therapeutic effect on severe and acute symptoms. A puzzling finding was that these levels were continued despite the fact that the patient's clinical condition, either in terms of anxiety, agitation, gross psychotic phenomena, or depression was steadily deteriorating (Cases I, VI, XI, and X).

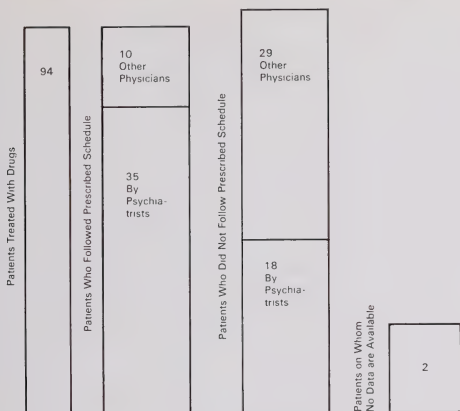
Laboratory Tests

Very few of the treating physicians included any laboratory evaluation or laboratory follow-up on their patients. Only 16 patients (18%) had any laboratory tests, blood examinations, or urine examinations prior to the use of the psychotherapeutic drugs. Six patients only had follow-up laboratory tests while they were receiving the drugs.

From discussions with colleagues in clinics and in the hospital it seems that the neglect of laboratory safeguards may be partially responsible for the low doses of drugs prescribed and there may be a relationship between the difficulty in obtaining laboratory tests and the low doses. Low doses are no safeguard for the serious side effects, since these are often not dose-dependent.

Patients' Attitudes toward Medication

A problem in evaluating the effectiveness of psychotherapeutic drugs, especially in ambulatory patients, has been the uncertainty about how regularly the drugs are taken (11, 12). Our results indicate that patients generally follow a very loose schedule on their own. For example, less than 50% of the patients in our sample took their medication in any regular way. A study of the possible factors influencing this focused on the physician prescribing the drugs and the supervision and explanations or instructions accompanying the pre-



Note: not to scale.

FIG. 4

scription. Of 45 patients (48%) who followed the prescribed schedule, 35 were being treated by psychiatrists and 10 by non-psychiatrists. Of 47 (52%) who did not take the medication as prescribed, 18 were treated by psychiatrists and 29 by non-psychiatrists (Fig. 4).

The fact that more patients followed the schedules of the psychiatrists than of the non-psychiatrists may reflect the closer relationship between the psychiatrist and his patient, or it may indicate a patient's greater willingness to accept this type of drug from a psychiatrist who is presumably more familiar with it.

There seemed also to be a correlation between the patient's understanding something about the drug and a more faithful adherence to treatment schedules. Of the 94 drug-users, only 33 had any knowledge or understanding of what the medication was for or what it might be expected to do. Among these 33 informed patients, 24 (73%) were "good adherers." Among the 61 uninformed patients, only 21 were good adherers (Fig. 5).

Individual Patterns of Use

Not only the doctors showed their individuality in choice and scheduling of the drugs but patients themselves evolved individual schedules, some of which seemed to be related to the patient's self-image and past experiences.

Case XV. The patient was a 36 year old woman who had had intermittent ambulatory psychiatric treatment for many years. As a child she had a bilateral mastoidectomy which became the core of her delusional system. She searched from doctor to doctor with the hope that one of them would undo the damage she had suffered by the operation.



Note: not to scale.

FIG. 5

During this searching she accumulated medications, all of which she took in a haphazard manner. Her dependence and wish for a magical solution were so great that she never completely discontinued any medication. She finally found the neurosurgeon who performed the original operation; when he would not help her, astasia abasia developed, she became very depressed, and she had to be hospitalized. On admission, she was taking meprobamate, chlordiazepoxide hydrochloride, chlorpromazine hydrochloride, amitriptyline hydrochloride, deprol, several antihistamines, propoxyphene hydrochloride* and aspirin.

Discussion

After fourteen years of extensive use of psychotherapeutic medication there seems still to be considerable confusion about the relative indications for the types of drugs, the dose schedules and the duration of treatment. It is apparent that most psychiatric patients today receive some type of medication and the indications are that this will increase towards 100%. It is thus all the more important to assess what we do know about their use and how this information is being applied.

If we follow the generally accepted "target symptom" model for choosing a drug (at the present time the choice is based on psychotic and non-psychotic anxiety, depression, agitation, mania or withdrawal, and not on nosology), then our referring doctors used the "wrong" drug most of the time. This was true even where combinations of drugs were used. The most striking finding was that even where the presenting symptom responsible for hospitalization was depression, the drug was a phenothiazine, usually not indicated for depression and perhaps even depressogenic in itself. Because we did not interview the referring physicians directly, we do not have a clear

* Darvon (Lilly).

answer to why this was so. In general, it seems that correlation between outstanding symptoms and choice of drug could not be clearly established. We have considered several possible explanations: 1) There is the possibility that our interest in nosology and our desire for a specific treatment method for a specific disease category outweighs our knowledge that this does not yet apply to the available medication in psychiatry. Perhaps a severe depression is overlooked because the overall picture is that of "underlying schizophrenia" (the category of most of our hospitalized patients) and depression is seen as a "minor" phase of the psychosis. 2) It is possible that our lack of full understanding of the relationships between anxiety and depression, or psychosis and depression, lead to the different approaches. Perhaps one person sees the depression occurring in the context of a schizophrenia, whereas another sees the schizophrenic reaction appearing in circumstances which do, or should expect to, cause depression. In this context, there is a growing interest in the psychodynamics and psychopathological background as a guide to the use of the drugs. Thus, manifest anxiety, or even disturbed behavior or thinking, when occurring in an atmosphere of loss (a depression-producing situation) might be treated with an antidepressant rather than an anti-anxiety drug) (13, 14). 3) A further possibility is in the confusion between anxiety and agitation and their occurrence in depression. Thus, agitation may be treated with a phenothiazine while the depression is overlooked. 4) Perhaps physicians and hospital staffs tolerate non-suicidal depression states better than they do active, anxious and agitated states. Certainly the former tend to a "quicker," "more peaceful" behavioral effect. 5) Perhaps physicians are less confident with antidepressants, which do not give the quick, readily observable dramatic results of tranquilizers, which have lag phases and clear the system slowly, and which are associated historically with unfortunate, dramatic and non-reversible tissue damage.

We have no ready explanation as to why, when drugs were used, they were used in too low a dose for too short a time, despite the fact that all the published data, as well as the drug company recommendations, are quite explicit on this point. Can it be that the doctors are not familiar with the drugs or are uncertain and uneasy about the side or toxic effects? Or did we see a selected group, so ill that early hospitalization was anticipated and the drugs were given only as a "holding" procedure? Or were the prescribing doctors reluctant to use drugs of this nature altogether?

When we examined the patterns of doctor-patient relationship and the supervision of the patient, we saw that those patients who were closely supervised, who had a close relationship with their doctor, and to whom the drug was given in the context of overall psychiatric care, took the drug more closely to the expected optimum schedule. In other words, "patient failure" may be the factor most responsible for the failure of drug treatment to reach optimum dosage for a long enough time period. Depressed, anxious or psychotic patients need close supervision and guidance. Every treatment method is placed by them in their own distorted view of the world. Thus medication may

be seen as a way of getting rid of them, as a sign of their hopeless state, or as a plot against them (in paranoia). And perhaps not the least important, the failure to achieve dramatic and total relief may be seen as a failure of omnipotence (of doctor) and a sign that "not enough" is being done or that the doctor "doesn't love me enough" to make him better right away. The physician, for his part, may feel frustrated and disappointed while waiting for the hoped-for results. Whatever the reasons, it is clear that many more patients are undermedicated than overmedicated. A failure to use the doctor-patient relationship in an understanding, supportive way, seems to be responsible for many drug treatment failures.

We were concerned by the lack of careful laboratory control of patients receiving potentially dangerous drugs. While we were pleasantly surprised at the almost complete absence of serious side or toxic effects, we feel that there is a false sense of security which is potentially explosive. Some system of toxicity control should be routine when these drugs are used.

The treatment of emotionally-ill patients has been changed dramatically since the introduction of psychotherapeutic drugs. Most notable has been the opportunity to reverse the hospital discharge rates and to treat vast numbers of patients in the community on an ambulatory basis. Our knowledge of the indications for, and actions of, psychotherapeutic drugs is still very elementary. Undoubtedly, as new data emerge, better and more specific agents will appear. However, current usage indicates that even what is known and what is available is not being applied properly. It is necessary for physicians to become more familiar with the indications and actions of these drugs, and to recognize that, contrary to some opinions (15) certain refinements in symptomatic diagnosis, and meticulous attention to the prescription of medication in the context of the overall care of the patient will greatly improve their effectiveness.

These observations do not necessarily constitute valid criticism of the way psychotherapeutic drugs are used. We are unable to say that this treatment is good or bad. We can say that it was consistently inconsistent. The explanations for this are not yet clear.

Summary

A study of the use of psychotherapeutic drugs prior to hospitalization indicated the following:

1. There was a high degree of inconsistency in choice of drug or drug-combinations, dosage schedules, duration of treatment, and care of the patient during the period of drug taking.

2. Although depression, with or without agitation, was the most frequent presenting symptoms, tranquilizers rather than anti-depressants were the more commonly used. Tranquilizers were often the only medication used in severely depressed and suicidal patients. If choice of drugs is to be based on the "target symptom" model, then most physicians used the "wrong" drug most of the time.

3. When tranquilizers alone were used, there was no consistent relationship between the clinical picture and the prescription of "major" or "minor" tranquilizers. There was no consistency in drug-combination choice in relation to the symptomatology.

4. Dosage schedules were usually below the recommended levels and rarely did they reach the accepted therapeutically effective range. There was often no dose adjustment in the presence of a changing clinical state.

5. Patients usually followed the physicians' recommendations in a haphazard manner. Those treated by psychiatrists were more observant of their schedules than those treated by non-psychiatrists. It appeared that the more the patient understood about the use of the medication the better he followed the recommendation.

6. There was a notable lack of careful laboratory control in patients receiving these potentially hazardous medications.

Some possible explanations for these puzzling patterns of psychotherapeutic drug use are presented.

ADDENDUM

Since this work was done, others have emphasized the legal considerations related to this (16).

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Coombs' Positive Hemolytic Anemia due to Penicillin

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While receiving massive penicillin therapy, a patient developed a Coombs' positive hemolytic anemia which remitted when the drug was discontinued. Only nine other cases of this occurrence have been reported. It is the purpose of this paper to describe the first such case seen at this Hospital and to discuss the immune mechanisms involved.

Methods

Standard direct and indirect Coombs' tests were performed with rabbit anti-human gamma globulin serum. O positive red cells were coated with penicillin according to the method of Ley, *et al* (1) by incubating with Alsever's solution and penicillin G in a concentration of 40–50,000 units per ml, the same patient's cells untreated being used as controls. Antibody elution was performed by the Rubin modification (2) of the Kidd ether method and by the heat elution method of Landsteiner and Miller (3). The patient's serum was tested against a panel of bromelain and polyvinylpyrrolidone treated cells in an autoanalyzer as described by Rosenfield *et al* (4). Serum and eluate were treated with 2-mercaptoethanol as described by Swanson *et al* (5).

Case Report

A 57 year old white woman (MSH #354138) was admitted to The Mount Sinai Hospital on February 17, 1967 for possible open heart surgery. A heart murmur had been noted for 15 years, but signs of congestive heart failure did not appear until 8 months prior to admission. She responded poorly to medical management and, following two episodes of pulmonary embolization, underwent cardiac catheterization at another hospital which revealed severe mitral stenosis with some regurgitation. There was no past history of rheumatic fever, hematologic disorders, drug allergy or asthma. The family history was not relevant.

Physical examination revealed a dyspneic, chronically ill-appearing woman with a regular pulse of 120, and blood pressure of 105/85. The neck veins were distended. The lungs evidenced bilateral wheezes and rhonchi. The heart was enlarged to the anterior axillary line with murmurs of mitral insufficiency and stenosis. The liver was tender and palpable 4 finger-breadths below the right costal margin. Hepatojugular reflux was present. There was no splenomegaly or significant lymphadenopathy. Peripheral pulses and neurologic examination were normal.

After medical management which included digitalis, mercurial, spironolactone and thiazide diuretics, coumadin and heparin, on March 14, the patient underwent mitral valve replacement with a Starr-Edwards valve. Total pump time was 80 minutes; there were no unusual problems encountered. Postoperatively, the patient breathed poorly on

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TABLE I
Antibiotic Therapy

Drug	Daily dose	Begun	Discontinued	Route
Penicillin.....	1.2 mega units	3-14	3-24	IM
Penicillin.....	30 mega units	4-20	5-12	IV
Ampicillin.....	800 mg	3-28	4-11	Nebulizer
Ampicillin.....	6 gm	4-12	4-20	PO
Ampicillin.....	600 mg	4-18	5-1	Nebulizer
Streptomycin.....	1 gm	3-14	3-20	IM
Colymycin.....	75 mg	3-26	6-1	IM
Colymycin.....	75 mg	6-8	6-23	IM
Keflin.....	4 gm	3-20	4-1	IV
Keflin.....	8 gm	4-2	4-12	IV

her own, and required a tracheostomy on the second postoperative day. Copious tracheal secretions persisted, and on March 19, x-ray demonstrated a right lower lobe pneumonia, which progressed to central necrosis and abscess formation. In spite of vigorous antibiotic therapy (Table I), suctioning and bronchoscopy with aspiration of mucous plugs, she continued to deteriorate. On April 17, a chest tube was inserted which drained foul-smelling greenish pus. Her condition stabilized, but because of persistent fever on May 1 she underwent rib resection with placement of a large bore chest tube and drainage of more purulent material. From this point on, her condition began to slowly improve, her fever disappeared, she began to gain weight. In addition to the previously mentioned drugs, she was also treated with KCl, Ferinsol,[®] Polyvisol,[®] chloral hydrate, Elavil,[®] Darvon,[®] Colace[®] and morphine. She had never taken alpha methyl dopa.

A falling hemoglobin which necessitated four transfusions at the time of her rib resection was attributed to a combination of infection and operative bleeding. When the anemia failed to improve subsequently, other studies were done which, for the first time, revealed evidence of a Coombs' positive hemolytic anemia, and hematologic consultation was requested. When seen on May 22, she appeared chronically ill. She no longer had distended neck veins. The heart was enlarged but was now free of murmurs. The liver was enlarged by 2 fingerbreadths, but again there was no splenomegaly. Studies detailed below implicated penicillin (which had already been discontinued) as the etiology of her anemia. No therapy was given, and her hemoglobin slowly returned to normal (Fig. 1).

Laboratory studies included normal or negative urinalysis, BUN, creatinine, calcium, phosphorus, glucose, SGOT, bilirubin, LE preparations, PPD intermediate skin tests, blood and urine cultures. Electrocardiograms demonstrated sinus tachycardia with varying ST segment and T wave abnormalities. Protein electrophoresis revealed diffusely increased gamma globulin (2.5 gm %). Cultures of sputum and pleural drainage consistently revealed *E. coli*, *Serratia*, *S. Aureus* and *Pyocyanus*; of 12 stool examinations for blood, 11 ranged from 0 to 2+ and one was 4+.

During the period of hemolysis, her peripheral smear revealed normochromic, nonfragmented red cells and occasional spherocytes. The mean corpuscular volume was 94, the mean corpuscular hemoglobin 28.5 and the mean corpuscular hemoglobin concentration 30.5. The white blood count was 15,600 (14% bands, 69% segmented neutrophils, 2% monocytes, 8% lymphocytes, and 7% eosinophils). Platelets were 620,000. Serum iron and iron-binding capacity, B₁₂ and folate levels were normal. Urine hemosiderin, plasma hemoglobin and methemalbumin were absent. Bone marrow aspirate was very cellular with numerous megakaryocytes, a myeloid-erythroid ratio of 1.6:1 and normal iron stores.

TABLE II
Agglutination Studies

	Normal RBC		Penicillin RBC	
	Spontaneous agglutination	Indirect Coombs'	Spontaneous agglutination	Indirect Coombs'
Patient Serum.....	0	0	+ (undil.)	+ (1/20)
Normal Serum.....	0	0	0	0
Ether Eluate.....	0	0	0	0
Heat Eluate.....	0	0	0	+ (1/5)

TABLE III
Lack of Antibody Inhibition by 2-Mercaptoethanol

	Concentration of serum or eluate				
	Undiluted	1/5	1/10	1/20	1/40
Patient Serum.....	+	+	+	+	0
+ ME.....	...	+	+	±	±
Eluate.....	+	+	0	0	0
+ ME.....	+	+	0	0	0

Indirect Coomb's tests were performed using penicillin coated RBC and the patient's serum or the heat eluate from her own RBC before and after incubation with 2-mercaptoethanol.

was not inactivated by treatment with 2-mercaptoethanol (See Table II and III).

Discussion

ANTIPENICILLIN ANTIBODIES

Ley, *et al* (1) were the first to describe hemagglutinating antibodies to penicillin-coated red blood cells in the sera of patients who had received penicillin therapy. Schwartz and Vaughan demonstrated antipenicillin antibodies in the sera of 9 of 27 (33%) patients who had recently received penicillin therapy without adverse reactions, and in 22 of 27 (81%) patients who developed symptoms of allergy to penicillin (8). Levine, using a more sensitive assay, found them in 100% of a group of 115 penicillin treated patients (9).

It now appears that penicillin G and several of its metabolites are antigenically active, and may induce several classes of antibodies (9, 10) even in the same patient. The benzylpenicilloyl group is the most potent haptene, and usually gives rise to 19S (IgM) antibodies which cause *in vitro* hemagglutination of penicillin-coated red cells, and are selectively inactivated by 2-mercaptoethanol. 7S (IgG) antibodies occur less frequently, are usually induced by other penicillin metabolites, "minor antigenic determinants," (9)

TABLE IV
Features of Penicillin-Induced Coombs' Positive Hemolytic Anemia

Sr. author	Dose (million units) per day	Interval to onset of hemolysis (days)	Duration of therapy (days)	Type of antibody identified	Clinical allergy	Other conditions
Ley ¹¹	18*	7	?	?	0	Fatal septicemia
Strumia ¹²	24*	10	28	?	Urticaria	Bacterial endocarditis
Van Arsdale ¹³						
1.	20	5	14	7S & 19S	0	Bacterial endocarditis
2.	30*	?	20	19S§	0	Septicemia, bacterial endocarditis?
Beardwell ¹⁴	10	?	26	?	0	Bacterial endocarditis
Petz ¹⁵	100	13	25	7S	Erythema, pruritis	Bacterial endocarditis
Swanson ⁵	40	8	1†	7S & 19S	Fever	Infected burn
Dawson ¹⁶	40	5	2‡	7S	0	Atrial septal defect repair, cardiopulm. bypass
Lai ¹⁷	30	7	7	7S	0	Disseminated tbc
Present case	30	10	24	7S & 19S	0	Prosthetic valve, lung abscess

* Probenecid given concurrently.

† Preceded by lower dose therapy for 5 days.

‡ Preceded by lower dose therapy for 2 days.

§ 7-S antibody was not excluded in this case.

|| Plus methicillin, 5 gm daily.

and can only be detected by the indirect Coombs' test using penicillin-coated red cells. IgA antibodies also occur. They correlate well with immediate hypersensitivity reactions, but do not appear to be hemagglutinins (9).

Mechanism of the Hemolytic Anemia

Some of the features of this syndrome are summarized in Table IV. The crucial factors seem to be two—a sufficiently high dose of penicillin to coat the patients' red blood cells *in vivo*, and the presence of 7-S antipenicillin antibody. (In Van Arsdale's case #2, an indirect Coombs' test was not performed with penicillin-coated red cells, so that the presence of 7-S antibody was not excluded.) This antibody appears in about $\frac{1}{3}$ of penicillin treated patients (9), and these are potential hemolyzers.

Once the coated red cells bind the 7-S antipenicillin antibody, they are subject to premature destruction by the reticuloendothelial system. The fact that this is not due to the penicillin coating *per se* was demonstrated by Swanson *et al* (5) who showed that Cr⁵¹-tagged, penicillin-coated red cells survived normally in a recipient without antipenicillin antibodies. The severity of hemolysis may depend on other factors, *e.g.* the presence of septicemia, bacterial endocarditis, valvular heart disease, cardiopulmonary bypass and prosthetic

valves (Table IV) all of which may shorten red cell survival. Some hemolysis may occur without a positive Coombs' test, as in the present case after June 3 (Fig. 1), and presumably in many mild cases of the syndrome.

Diagnosis

It is likely that this syndrome has occurred far more often than the total of ten reported cases suggests. It is a diagnosis that should be considered whenever anemia develops in a patient receiving high dosage penicillin therapy, for a change in antibiotics may obviate the need for transfusions. Because of their frequent occurrence, the presence of antipenicillin antibodies in the serum of a patient receiving penicillin and manifesting a Coombs' positive hemolytic anemia does not prove that penicillin is the etiologic factor. All evidence other than antibody elution from the patient's cells is only suggestive; the present case illustrates the superiority of heat elution for diagnosis of this disease.

Finally, there is no contraindication to conventional dose penicillin therapy (*e.g.*, for pharyngitis) in a patient who recovers from the hemolytic anemia, because such therapy will not produce significant *in vivo* coating of the patient's red cells. Petz and Fudenberg (15) had to challenge their patient with 100 million units of penicillin per day in order to reproduce the syndrome.

Summary

A case of Coombs' positive hemolytic anemia due to penicillin is described. Massive penicillin therapy and 7-S antipenicillin antibodies are the prerequisites for this syndrome. Conventional penicillin therapy can be given safely to a patient who recovers from the hemolytic anemia.

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Exercise in Normal Dogs under Chloralose and Urethane Anesthesia

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This study was undertaken to determine in anesthetized dogs, the effects of exercise on commonly used indices of left ventricular function. Exercise in the form of muscular contractions can be produced in anesthetized dogs by repetitive electrical stimulation of the leg muscles. This technique of exercise production affords a simple and readily available method for the study of cardiac function in animals during exercise. Few studies of left ventricular function during exercise have been performed previously in animals (1-3). No studies have been reported on the effects of exercise in *anesthetized* animals. Studies of left ventricular function under these circumstances are of interest for two reasons. Such studies add to the limited information now available regarding left ventricular performance during exercise, and may serve as controls for future studies of the effects of various interventions upon the left ventricular performance of anesthetized dogs. A mixture of alpha chloralose (chloraloseane) and urethane (ethyl carbamate) was chosen as the anesthetic agent in this study. These drugs are widely used for anesthesia in physiological studies since neither drug appears to block the action of the autonomic nervous system (4, 5).

Method

Nine healthy female mongrel dogs, all under two years of age, weighing from 16 to 24 kg, were studied. The dogs were initially anesthetized with a mixture of alpha chloralose (100-150 mg/kg) and urethane (1 gm/kg). Supplemental doses were given to assure a stable level of anesthesia but no additional doses of anesthetic were given between the time baseline pressures were recorded and the experiment was terminated. The dogs were intubated with an endotracheal tube and permitted to spontaneously breathe room air. A 12 lead electrocardiogram was recorded. Retrograde left heart catheterization was performed under fluoroscopic control with a double lumen cardiac catheter. The proximal lumen was positioned in the central aorta and the distal lumen in the left ventricle. Right heart catheterization was also performed and a catheter was positioned in the main pulmonary artery.

On two occasions, a specially prepared latex balloon sealed to a polyethylene

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catheter was positioned in the esophagus above the diaphragm in order to measure approximate intrapleural pressure (6).

Pressures were determined with Statham P23 D strain gauge transducers and were recorded on an eight channel oscillographic photographic recorder. The top of the fluoroscopic table was taken as the zero level for all pressures. Oxygen consumption was determined, after a preliminary check for leaks, by having the animals rebreathe 100% oxygen from a nine liter Collins spirometer with CO₂ adsorber. Values were adjusted to standard temperature and pressure. A 10 minute equilibration period was allowed prior to the determination. Aortic and pulmonary arterial blood samples were drawn simultaneously and oxygen content in duplicate determined on a Van Slyke manometric instrument. Cardiac output was then calculated by the Fick principle. Exercise, in the form of repetitive muscular contraction, was produced by electrical stimulation using a Grass stimulator at four shocks per second of 80 volts and five millisecond duration. Needle electrodes were inserted into the muscles of the upper portions of one hind limb alone, or into one hind limb and one fore limb. After 10 to 15 minutes of steady exercise, pressures, oxygen consumption and cardiac output were again measured.

Calculations were made as follows (7).

$$\text{Total Peripheral Resistance (dynes sec cm}^{-5}\text{)} = \frac{P_{Ao}}{C.O.} \times 79.92$$

Left Ventricular Minute Work (Kg-m/min)

$$= \frac{(C.O. \times 1.055) (P_{Ao} - LVEDP) 13.6}{1,000}$$

where:

P_{Ao} = Mean Aortic Pressure (mmHg)

C.O. = Cardiac Output (liters/min)

LVEDP = Left Ventricular End Diastolic Pressure (mmHg)

1.055 = Specific Gravity of Blood

13.6 = Specific Gravity of Mercury

79.92 = Conversion Factor

The kinetic component of minute work ($1/2mV^2$) was not calculated. According to Chapman and associates, kinetic work accounts only for 10% of total work even during exercise (8).

Results

Pressures, outputs, and functional indices are shown in Table I.

Pre-exercise control left ventricular end-diastolic pressures (LVEDP) averaged 8 mmHg with a range of 6 to 11 mmHg. Left ventricular end-diastolic pressure fell in all but one animal during exercise (Fig. 1). The average post-exercise value was 5 mmHg with a range of 0 to 8 mmHg ($.02 > P > .01$).

Average effective intrapleural pressure, in the two dogs in which it was measured, changed from a resting value of minus 1.2 mmHg to an exercise value of plus 0.3 mmHg.

TABLE I
Hemodynamic Measurements at Rest and during Exercise.

Dog number	Aortic pressure (mm Hg)		Mean aortic pressure (mm Hg)		Left ventricular systolic pressure (mm Hg)		Left ventricular end diastolic pressure (mm Hg)		Cardiac output (liters/min)		Stroke volume (ml/beat)		Heart rate (beats/min)		Peripheral resistance (dynes sec cm ⁻⁵)		Left ventricular minute work (kg m/min)		Oxygen consumption (ml/min)		Arteriovenous oxygen difference (ml/100 ml)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
1	139/95		116		145	175	10	8	4.2	6.4	43	55	100	115			6.4	126	289	3.0	4.5	
2	165/118		140		165	134	8	3	3.1	3.4	22	23	140	155	3600		5.9	98	217	3.2	6.4	
3	117/72	130/78	88	99	129	129	8	5	3.2	5.6	18	29	170	190	2200	1400	3.7	122	445	3.8	8.0	
4	156/108	121/72	122	93	172	142	11	0	7.5	7.7	41	49	180	180	1300	1000	12	158	528	2.1	6.9	
5	173/104	156/69	137	107	163	142	10	7	4.2	7.6	24	42	170	180	2600	1200	7.7	11	130	575	3.0	7.6
6	171/98	158/71	122	111	175	165	6	2	4.3	8.7	25	47	170	185	2300	1000	7.2	14	174	720	3.9	8.3
7	159/95	161/111	126	136	164	169	7	7	4.5	7.0	26	41	175	170	2200	1600	7.7	12	146	850	3.2	12.2
8	159/102	147/90	121	107	156	140	6	4	4.0	5.5	20	28	200	200	2400	1600	6.6	8.2	109	382	2.7	6.9
9	153/106	153/70	133	125	156	144	9	8	3.0	6.3	19	29	160	220	3600	1600	3.4	11	130	717	4.3	11.4
Average	155/100	147/80	123	111	158	149	8	5	4.2	6.5	26	38	160	180	2500	1300	5.6	11	133	525	3.2	8.0

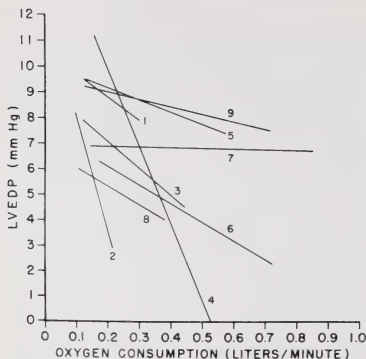


FIG. 1. The effect of exercise on left ventricular end-diastolic pressure is shown in relation to oxygen consumption at rest and during exercise. A slight fall in left ventricular end-diastolic pressure during exercise was noted in all but one dog, though the magnitude of change was unrelated to the degree of increase in oxygen consumption.

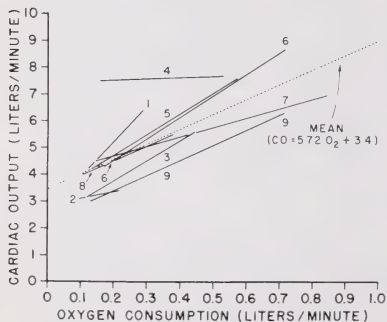


FIG. 2. Relation of cardiac output to oxygen consumption at rest and during mild to moderate exercise. Cardiac output increased in all animals. The relationship of increase in cardiac output to increase in oxygen consumption, calculated from the data by the method of least squares, is shown by the interrupted line the equation of which is: C.O. (liters/min) = $5.72 O_2$ (liters/min) + 3.4.

Resting oxygen consumption ranged between 98 and 174 ml/min with an average of 133 ml/min. Oxygen consumption rose with exercise to an average of 525 ml/min with a range of 217 to 850 ml/min.

Resting cardiac output averaged 4.2 liters/min with a range of 3.1 to 7.5 liters/min. During exercise, cardiac output increased to an average of 6.5 liters/min with a range of 3.4 to 8.7 liters/min (Fig. 2). The relationship of cardiac output to oxygen consumption, calculated from the data by the method of least squares, was:

Cardiac output (liters/min)

$$= 5.7 \text{ Oxygen consumption (liters/min)} + 3.4.$$

Arteriovenous oxygen difference before exercise ranged from 2.1 to 4.3

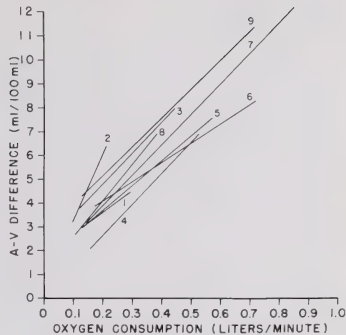


FIG. 3. Relation of arterio-venous oxygen difference to oxygen consumption at rest and during exercise. The A-V oxygen difference widened in all animals. This increased A-V oxygen difference with exercise is a normal response indicating that oxygen utilization during exercise was in excess of the rise in cardiac output.

vol % with an average of 3.2 vol %. During exercise, the average arterio-venous difference widened to 8 vol % with a range of 4.5 to 12.2 vol % (Fig. 3). All dogs manifested full arterial oxygen saturation both at rest and during exercise.

Response of blood pressure to exercise was variable. Five animals showed a fall of both systolic and diastolic pressure and two animals showed a rise. Central aortic pressure at rest averaged 154/100 mmHg with a range of 117/72 to 173/104 mmHg. After ten minutes of exercise, average aortic pressure had fallen to 147/80 mmHg with a range of 121/72 to 161/111 mmHg. Average mean central aortic pressure fell during exercise from 123 to 111 mmHg. Whether blood pressure fell or rose did not seem to be related to the severity (as judged by the oxygen consumption) of the exercise imposed.

The average heart rate just after induction of anesthesia was 135 beats/min. This rate increased during the period of cardiac catheterization (approximately 45 minutes) to an average rate of 160 beats/min just before exercise, with a range of 100 to 200 beats/min. During exercise, the average heart rate increased to 180 beats/min with a range of 115 to 220 beats/min. Three of the nine animals showed no increase in heart rate, and the increase in the others was not related to increase in oxygen consumption.

Peripheral resistance fell during exercise in each animal. Average resting value was 2,500 dynes sec cm^{-5} with a range of 1,300 to 3,600 dynes sec cm^{-5} . During exercise, the average peripheral resistance fell to 1,300 dynes sec cm^{-5} with a range of 1,000 to 1,600 dynes sec cm^{-5} .

Stroke volume increased during exercise in all animals. Stroke volume averaged 26 ml/beat before exercise with a range of 10 to 43 ml/beat. During exercise, the average stroke volume increased to 38 ml/beat with a range of 23 to 55 ml/beat.

Left ventricular minute work rose during exercise in all but one dog. Resting minute work increased from an average of 5.6 Kg-m/min with a range of

3.4 to 7.7 Kg-m/min to an exercise value averaging 11 Kg-m/min with a range of 7.7 to 14 Kg-m/min.

Discussion

It would appear from this study that the use of chloralose-urethane anesthesia does not impair the performance of the heart of normal dogs during exercise as judged by the rise in cardiac output and left ventricular minute work and the fall in left ventricular end-diastolic pressure.

A decrease in left ventricular end-diastolic pressure during exercise was a consistent finding and occurred in spite of a rise in stroke volume and a rise in left ventricular minute work. Previous investigations in dogs have not shown a decrease of left ventricular end-diastolic pressure during exercise. Gregg (1), in dogs, reported no correlation between end-diastolic pressure and exercise. Nevertheless, review of his graphs showed a fall in end-diastolic pressure in three of five dogs and no change in one. Rushmer and associates found a reduction of left ventricular diastolic pressure during exercise in some dogs, but this was "not uniformly observed" (2). Intrapleural pressure changes did not account for the observed fall in end-diastolic pressure during exercise in our study, since measurement of average intraesophageal pressure showed no increase in negative pressure with exercise. Since the completion of this study*, a decrease or little change of left ventricular end-diastolic pressure during exercise has been reported in normal patients (9).

Consistent with the observation of a fall in left ventricular end-diastolic pressure with exercise is the previously demonstrated fall in left ventricular end-diastolic *volume* (2, 8, 10) since, in general, ventricular diastolic volume and pressure vary in the same direction.

The fact that end-diastolic pressure as well as end-diastolic volume have been found to be less during exercise than at rest, at a time when stroke work is increased, gives more evidence for the concept that exercise imposes some functional difference on the nonfailing ventricle. The ventricular function curve for exercise thus may be visualized as lying above and to the left of the curve for rest in keeping with Sarnoff's (11) and Sarnoff and Berglund's (12) concept of a family of curves, each one representing a different set of conditions under which the ventricle is operating.

The relationship of cardiac output to oxygen consumption was similar to that found by Barger and associates (3) in unanesthetized dogs, although the resting output of our animals was somewhat higher and the increase of cardiac output per unit increase in oxygen consumption was a little less. Thus, Barger and associates (3) found:

Cardiac Output (liters/min)

$$= 6.95 \text{ Oxygen Consumption (liters/min)} + 1.85$$

whereas we found:

* Abstract, Clinical Research 13: 529, 1965

Cardiac Output (liters/min)

$$= 5.72 \text{ Oxygen Consumption (liters/min)} + 3.4$$

Therefore, from these studies, a normal dog generally should show an increase in cardiac output of about 6 to 7 liters for each liter increase in oxygen consumption. There is, however, a wide range of variation so that one cannot predict the increase in cardiac output for any individual dog.

Arteriovenous oxygen difference increased in each dog during exercise. In human beings, Donald and associates (13) found that the arteriovenous oxygen difference was related to oxygen consumption in the following manner:

$$\text{A-V difference} = \frac{18.77 \text{ O}_2/\text{m}^2}{\text{O}_2/\text{m}^2 + 694.44}$$

where:

O_2/m^2 is oxygen consumption in ml/min/sq meter of body surface.

A-V difference is in ml of oxygen per 100 ml of blood.

Our value fit Donald and associates' (13) reasonably well (Fig. 4).

With regard to the systemic blood pressure response to exercise, both in awake dogs and human beings, reports in the literature indicate that a rise is usually encountered, although there is great individual variation (2, 14, 15). In this study, average mean aortic pressure fell from 123 mmHg to 111 mmHg although mean aortic pressure rose in several animals. The predominant decrease of pressure may have been due to greater vasodepressor effects from the anesthetic, or to absence of psychogenic factors normally present in awake exercising animals and human beings.

A rise in heart rate and stroke volume as well as a fall in peripheral resistance associated with exercise was also noted by Barger and associates (3). Rushmer and associates (2), however, found that the main compensatory change with exercise in the awake dog was an increased heart rate with little or no change in stroke volume.

Left ventricular minute work increased during exercise in all but one dog.

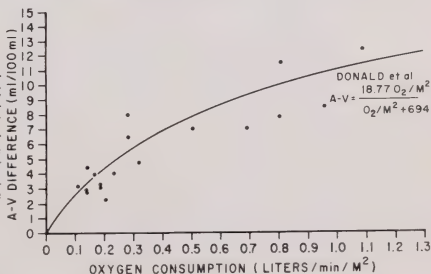


FIG. 4. Comparison of A-V oxygen difference at rest and during exercise in the present study (single points) with data obtained by Donald *et al* (13) in awake, exercising human beings (curve). Note that the points of the present study in dogs coincide reasonably well with the curve in patients. The equation for this curve is shown.

Gregg and associates (1) also found some variation in response. In his group, four of five dogs showed an increase in left ventricular minute work. One showed a fall of about 50%. Donald and associates (13) summarized their results and compared them with those of Dexter *et al* (7) and those of Riley *et al* (15) and found a rather uniform increase in left ventricular minute work associated with exercise in human beings.

Resting heart rate and cardiac output in the anesthetized dogs in this study were somewhat higher than the resting values observed by Gregg and associates (1) in unanesthetized dogs. High resting mean aortic pressure was found in this study as well, but values were no higher than resting pressures in the unanesthetized dogs observed by Gregg (1). Both chloralose and urethane according to some observers cause an elevation of blood pressure (4, 16). Van Citters and associates (17), however, noted no tachycardia and only transient changes in blood pressure and cardiac output following chloralose anesthesia in dogs.

Summary

Left ventricular pressures and flows during exercise were studied in nine normal dogs anesthetized with a chloralose-urethane mixture. Exercise was produced by repetitive electrical stimulation of the leg muscles. A statistically significant fall in left ventricular end-diastolic pressure during exercise was found. Cardiac output, left ventricular minute work, arteriovenous oxygen difference, stroke volume, and heart rate increased during exercise; peripheral resistance and blood pressure fell. The hemodynamic changes during exercise were consistent with those found in awake, trained animals and in normal patients. No evidence of impaired left ventricular function due to anesthesia was apparent.

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Bone Tumors of Periosteal Origin

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Introduction

Differential diagnosis of neoplasms involving bone requires careful clinical analysis and critical evaluation of roentgenographic and pathological findings. Although neoplastic and inflammatory alterations often produce easily recognizable effects, the response of bone to trauma, infections, inflammations, and affections (i.e. vascular, reticular, fibrous), is frequently nonspecific. For example, lytic and sclerotic lesions, as well as general osteoporosis and alterations in trabecular architecture can reflect responses ranging from general metabolic changes such as thyroid, pituitary and parathyroid to specific diseases such as Hodgkin's disease, reticuloendotheliosis, and angio-mas.

Accurate analysis of clinical findings and roentgenographic changes, therefore, must be based upon an understanding of basic bone pathology and physiology. This discussion will attempt to briefly classify bone tumors of periosteal origin and to clarify their clinical and pathological characteristics to aid in differential diagnosis and treatment.

Periosteum, derived from mesenchyme, is a pluripotential tissue (1), and can give rise to bony, cartilagenous or fibrous lesions.

On histological examination, the periosteum is composed of two layers: a fibrous outer portion and fibrocellular inner or cambium layer. This distinction is best seen in children. In adults, the periosteum is inactive and no osteoblastic activity is seen (2), except during stimulation such as fracture, infection or neoplasm.

The cellular element of the periosteum is the fibroblast. This ubiquitous mesenchymal cell, so aptly shown by Basset (3), can on certain milieu stimulation develop into bone, cartilage, or fibrous tissue. It is, therefore, not unexpected to see periosteally-derived neoplasms of these tissues.

Parosteal Osteogenic Sarcoma

The bony example of the periosteal tumors is the parosteal osteogenic sarcoma. This lesion is considerably rarer than the intramedullary variety of osteogenic sarcoma and occurs predominantly in the 3rd and 4th decade of life as contrasted to the latter which is seen most commonly in the 2nd decade (4).

The lesion is most commonly seen in the distal femoral metaphysis, but the other long bones have been affected. Symptoms begin insidiously and progress slowly. It may take years before the tumor is diagnosed and because of such symptom paucity, the mass may reach extensive proportion before the patient seeks medical attention.

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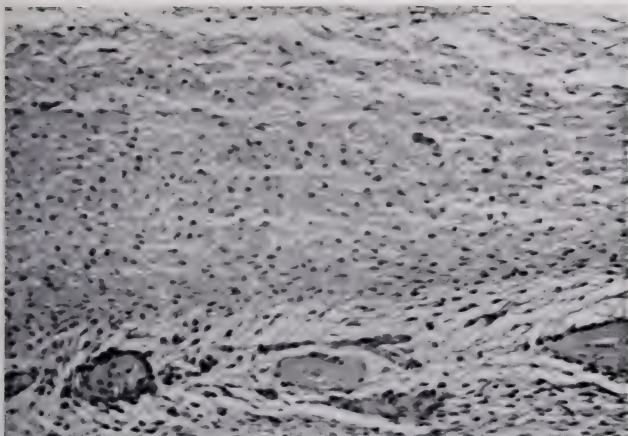


FIG. 1. Periosteal bone formation. The outer fibrous portion (a) appears dense and collagenous. The cambium or inner layer (b) contains spicules of new bone.

TABLE I
Bone Tumors of Periosteal Origin

Malignant	Benign
Parosteal Osteogenic Sarcoma	Periosteal Chondroma
Periosteal Chondrosarcoma	Periosteal Desmoid
Periosteal Fibrosarcoma	

Even when the tumor is large, the general condition of the patient is satisfactory. The skin overlying the tumor may be stretched, but is not adherent. Often, there is no increase of temperature or increased epidermal vascular pattern typical of osteogenic sarcoma.

On roentgenogram the lesion is seen most commonly oriented to the posterior cortex of the distal femoral metaphysis. There is usually no intramedullary encroachment, but this has been known to occur. The impression is that the lesion encircles, rather than erodes the bone. The tumor appears as a radiopaque shadow which is homogeneous or associated with lucent defects representing cartilagenous or fibrocartilagenous deposits. There is an inverse relationship between the homogeneity of the lesion and its rate of growth and invasiveness (5). The tumor grows slowly and continuously with perifocal areas of expansion, producing a lobulated appearance with growth directed into the peripheral soft tissues rather than into bone.

On gross pathological examination, the lesion is variable. Usually it appears lobulated, with cartilagenous elements oriented to the periphery. Centrally the lesional tissue is bony hard. The surface of the tumor is smooth and covered with a pseudocapsule. The tumor infiltrates between muscle planes and sometimes invades the muscle proper (4). The tumor is attached to the parent bone by a broad base.

The micropathological appearance varies from lesion to lesion depending upon whether one studies material from a recurrence, different areas from a given lesion, or whether the tumor is of relatively high or low malignancy (5).

The tissue is composed of a meshwork of relatively mature trabeculated bone within a spindle cell stroma. This stromal cell tissue is the key to diagnosis. Multiple sections must be studied because of the variability from one area to another. The central zones which are highly radiopaque are characterized by compact osseous tissue with narrow intertrabecular spaces within which is poorly vascularized fibroadipose tissue. As one looks towards the pe-

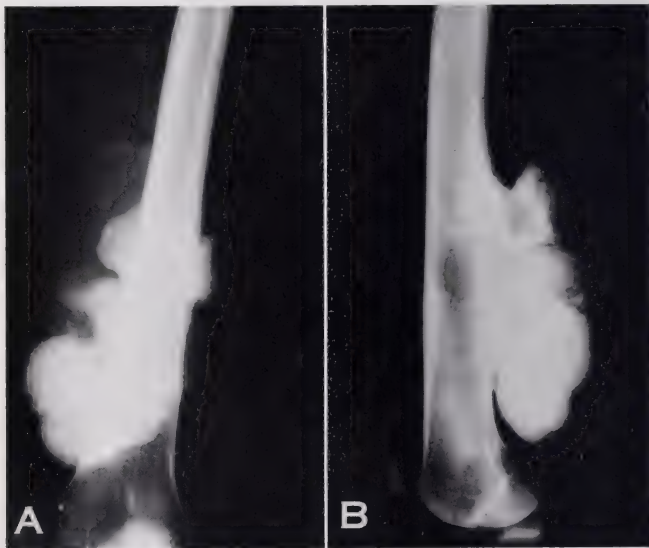


FIG. 2a. Parosteal osteogenic sarcoma. Note the characteristic lobulated appearance, density and areas of lucency indicating presence of cartilage within the mass.

FIG. 2b. The mass has a broad-based posterior origin. There is no evidence of intramedullary intrusion.

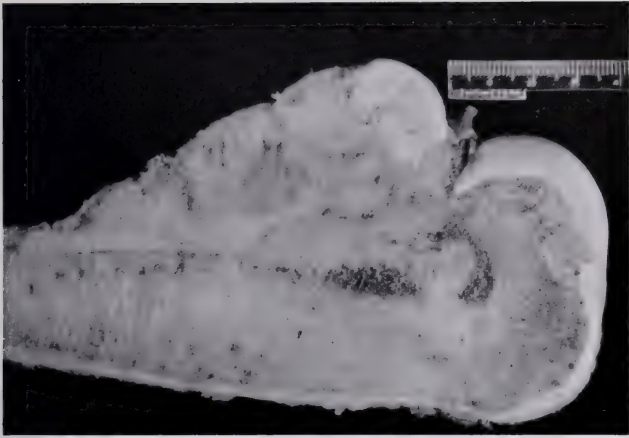


FIG. 3. Parosteal osteogenic sarcoma of distal femur. The lesion is composed of sclerotized densely packed tumor bone.

riphery, the intertrabecular spaces are wider and more cellular. Spindle cells predominate and the general pattern is fibrosarcomatous. If tissue from a recurrence is examined there is generally noted an accentuation of malignant characteristics.

TREATMENT

Amputation of the affected limb is the treatment of choice in high malignancy (approximately 25% of all cases). Amputation should take place as soon as the diagnosis is established. In cases of low malignancy, local block resection is preferred, if feasible (4).

Periosteal Chondroma

The periosteal chondroma develops in relation to the periosteum and tends to invade the underlying bone cortex, but usually does not break through into the medullary cavity (5). The lesion is uncommon and usually appears solitary. It occurs mainly in middle-aged or young adults and rarely children. Anatomically, the lesion is oriented to the shaft of a long or short tubular bone.

On clinical examination, the lesion appears indolent. There is little complaint of pain or tenderness; the only finding is a tumor which may have been present for months or years.

On roentgenograph one may observe only a faint soft tissue shadow. The tumor may be overlying a shallow cortical indentation with a sclerotic

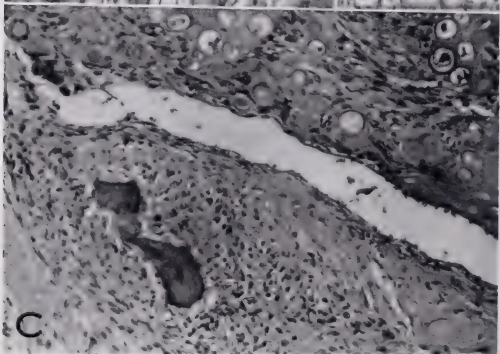
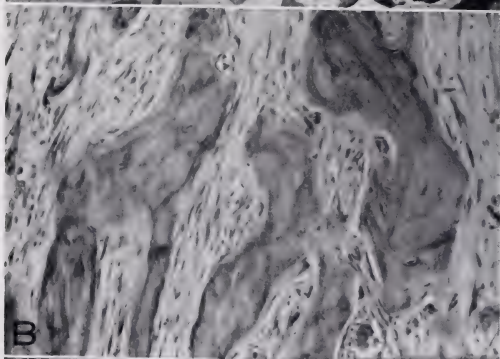
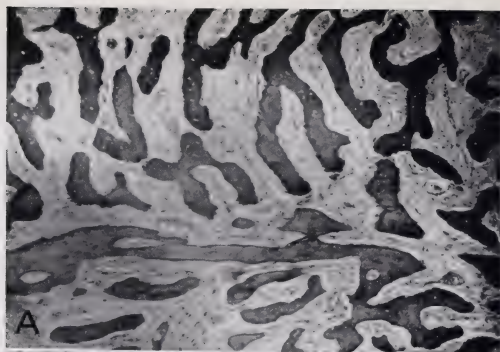
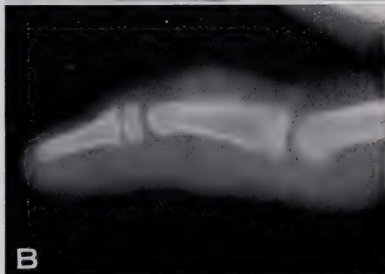


FIG. 5a. Periosteal chondroma. This mass at the dorsum of the index finger was painless and had been noted for three months.



FIG. 5b. A soft tissue mass is present oriented to the cortex of the middle phalanx. The bony cortex in apposition appears mildly sclerotized.



base. Foci of radiopacity may be noted, reflecting calcification or ossification, and is, therefore, important in the diagnosis of this lesion.

On gross examination, the lesion appears lobulated and is enclosed by a fibrous capsule. On sectioning, the cartilage appears bluish white and depending upon the degree of calcification or ossification, may feel gritty.

Micropathological examination reveals the division of the lesional tissue into lobules, as is common in all tumors of cartilage derivation. The cartilage of a periosteal chondroma is more cellular than that of a solitary enchondroma of a phalanx, metacarpal, or metatarsal bone. However, it is not as cellular as cartilage evolved from a solitary enchondroma of a long bone (5).

TREATMENT

Removal of the cartilaginous tumor and the overlying periosteal roof is considered adequate. If the bony cortex is eroded, then curettage of the

FIG. 4a. Parosteal osteogenic sarcoma. The tumor bone is oriented at right angles to the cortical bone. The tumor bone is well organized and the stroma appears benign.

FIG. 4b. This illustrates the importance of multicentric biopsy of bone lesions. Here the stroma has a definite sarcomatous appearance.

FIG. 4c. Parosteal osteogenic sarcoma. Note area of primitive cartilage formation, fibrosarcomatous stroma and appearance of frank malignancy.

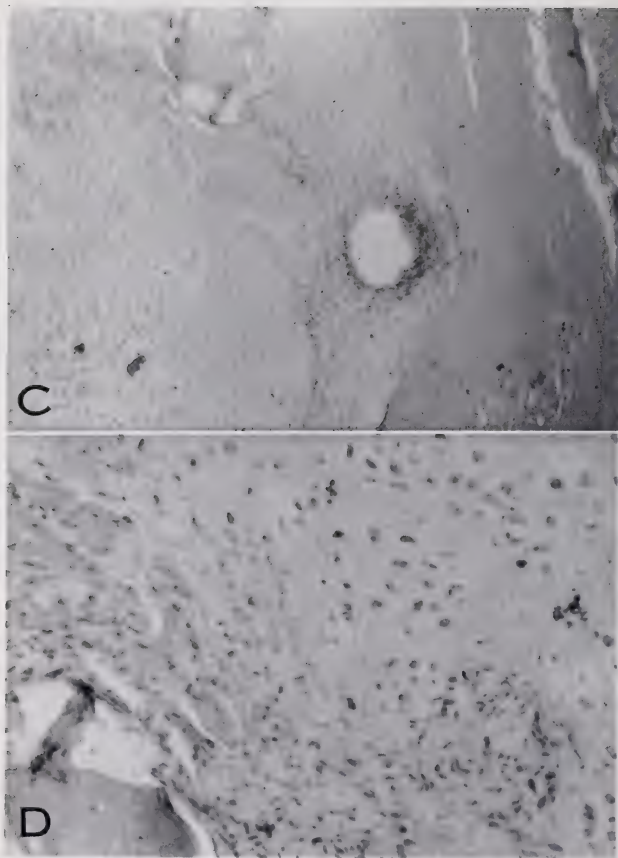


FIG. 5c. Periosteal chondroma. Note relation of bone, periosteum, and cartilage. Compare with Fig. 6a.

FIG. 5d. Higher magnification illustrates clearly benign appearance of immature cartilage cells in close association with periosteum.

affected bone is indicated. Block resection of the tumor and bony cortex is occasionally required.

Periosteal Chondrosarcoma

The periosteal chondrosarcoma is the cartilaginous analog of the parosteal osteogenic sarcoma. Similarly, it is the malignant counterpart of the periosteal chondroma (5). This tumor tends to invade the bony cortex and may enter the medullary cavity.

Micropathological examination reveals plump cartilage cells, often multinuclear, with some bizarre forms. The findings are not unlike those noted in intramedullary chondrosarcomata.

TREATMENT

Amputation of the affected part is carried out if local block resection is not feasible. In general, the prognosis for eradication of this lesion is good.

Periosteal Desmoid Tumor

The periosteal desmoid tumor is of fibrous origin and is benign. It is a rare lesion, found in children and young adults in association with periosteum and localized destruction of bone (6).

Kimmelsteil and Rapp reported this tumor in four males 8, 16, 19 and 20 years of age. Two patients had a history of trauma (7).

The tumor derived from periosteum is well-delimited and on gross examination appears firm and pinkish grey. On microscopic examination, much collagen and many fibrocytes are noted. Mitotic figures are few. It is important not to confuse this entity with a low grade fibrosarcoma.

On x-ray, the lesion resembles a fibrous cortical defect. The bony cortex is eroded and the lesion appears to be contained by a sclerotic border.

TREATMENT

Excision of the lesion is recommended and if adequate, recurrence is not expected.

Fibrosarcoma

Fibrosarcoma derived from periosteal fibrous elements is an unusual lesion. The usual appendicular fibrosarcoma is defined as fibroblastic connective tissue sarcoma developing endosteally. There are well-differentiated, and frankly anaplastic fibrosarcomas. Prognosis depends upon the histologic grading of the tumor.

Most patients with fibrosarcoma are young or middle-aged adults. There is no apparent sex predilection. The tumor tends to grow slowly and may become manifest only by sudden increase in growth; pain is not an important feature.

On x-ray one observes a soft tissue mass oriented to the cortex of a long bone with underlying sclerosis. Even if the lesion penetrates into the

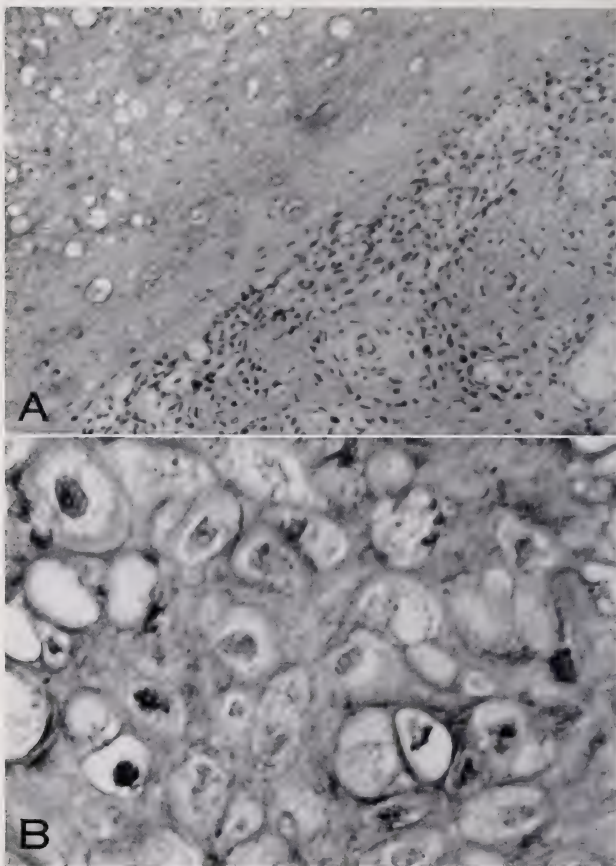


FIG. 6a. Periosteal chondrosarcoma. Chondrosarcomatous tissue is directly apposed to the periosteum which in this instance is highly cellular.

FIG. 6b. Periosteal chondrosarcoma. The cartilage cells are variegated in appearance and closely packed. The appearance is frankly malignant.



FIG. 7a. Periosteal desmoid tumor. The lesion is oriented to the cortex of the distal femoral metaphysis. The border is sclerotic and radiographically resembles the so-called fibrous cortical defect of bone.

bone, there is an underlying zone of reactive sclerosis. There is usually little difficulty in differentiating the periosteal fibrosarcoma from that arising endosteally.

On gross examination, the lesion is firm and may have muscle or fat adherent to its outer surface (5). On sectioning, the cut surface is white or greyish white and whorled tissue bundles, characteristic of fibrous lesions are noted. The more cellular lesions appear fleshy and grey. There is no clearly defined capsule.

On micropathologic examination, as noted previously, the lesion is well- or poorly-differentiated. In the well-differentiated lesion there is abundant collagen, few mitotic figures, and large adult-appearing fibroblasts. These cells are larger and more drawn out than the normal adult fibroblast.

In the poorly-differentiated lesion malignancy is evident; there is variation in cell size and staining properties. Tumor giant cells are seen and mitotic figures are frequent. The cells appear crowded and little fibrillar intercellular material is found. Some areas are frankly anaplastic.

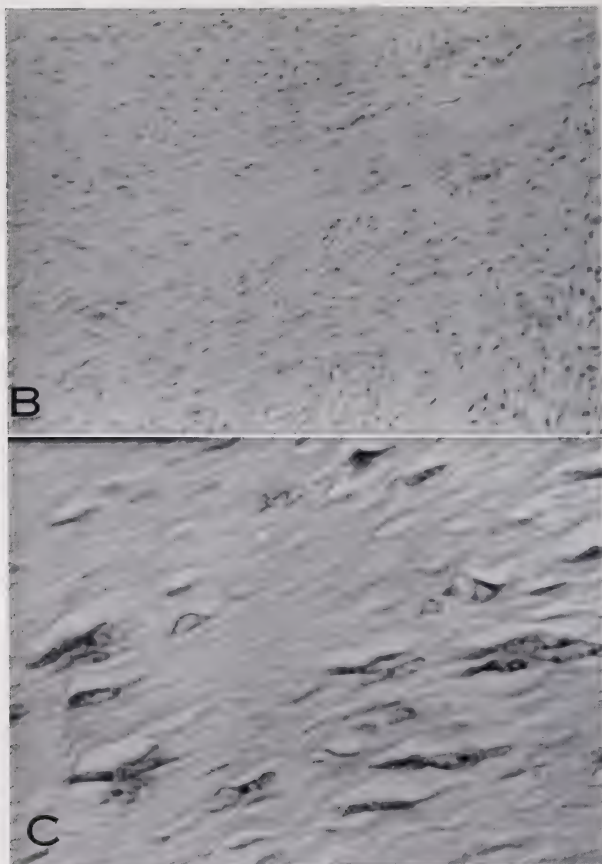


FIG. 7b. Periosteal desmoid. Collagen is abundant and the cells appear uniform.
FIG. 7c. Higher magnification of Fig. 7b. Note the abundant fibrillar collagen and elongated fibroblastic elements.

TREATMENT

Preferred treatment of periosteal fibrosarcoma is amputation of the part, unless there is confidence that the affected soft tissue and bone area can be radically excised without contamination of the surgical field.

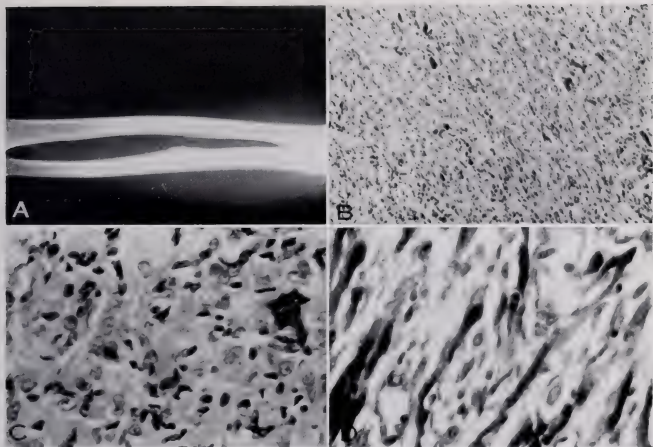


FIG. 8a. Periosteal fibrosarcoma. The lesion involves the midshaft of the ulna. Note the deposition of sublesional periosteal new bone.

FIG. 8b. Periosteal fibrosarcoma. The field is cellular, demonstrating scant collagen, tumor giant cells, and spindle cell elements.

FIG. 8c. Higher magnification of Fig. 8b reveals cellular characteristics of malignancy, *i.e.* variation of size and staining quality. Note the large dark-staining tumor giant cell.

FIG. 8d. Periosteal fibrosarcoma. Note the elongated fibroblastic elements. Many have dark-staining nuclei and abundant chromatin.

Periosteal Fibrosarcomas

Periosteal fibrosarcomas are usually poorly differentiated, have a high rate of recurrence and a strong tendency to metastasize. However, metastasis does not take place early, so that if the tumor is adequately treated at the first intervention the prognosis may be cautiously optimistic (5).

Discussion

It is important to delineate the tissue of origin of bone neoplasms. The fact that bone-forming sarcomas may also contain considerable areas of cartilage or solely contain fibrosarcomatous elements should not confuse the diagnosis.

Endosteal bone sarcomas including osteogenic sarcoma, central chondrosarcoma, and fibrosarcoma, generally have a poor overall prognosis. These lesions require radical surgical management, almost always ablation of the part. Generally, no more than 5 to 10% of those affected are permanently relieved.

The periosteal counterparts of the aforementioned tumors are, in comparison, less aggressive and relatively indolent. The clinical behavior of

the parosteal osteogenic sarcoma is different from that of the endosteal variety. Further, the treatment may require only local radical surgery rather than ablation of a limb. The same holds true with the other periosteal malignancies.

The prognosis following adequate treatment of malignant periosteal tumors is significantly better than their endosteal analogs. Cure rates range from 25 to 50% in various reported series.

Summary

The histology and histopathology of the periosteum have been discussed. It has been shown that this tissue can give rise to neoplasms peculiar to its pluripotential capabilities.

The prognosis for malignant lesions such as parosteal osteogenic sarcoma, periosteal chondrosarcoma, and periosteal fibrosarcoma, is better than that for endosteal neoplasms. Therefore, it is useful to classify neoplasms of bone not only by tissue of origin, but site of development as well.

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Unusual Problems in Surgery

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Indirect Traumatic Diaphragmatic Hernia. Typical and Unusual Features in Two Cases.

In an age of violence and high velocity impact forces such as automobile and other accidents of modern life, the surgery of trauma occupies an increasingly prominent role. The more obvious and frequent cranial and extremity injuries are readily recognized. Direct diaphragmatic injury due to penetrating wounds is usually automatically suspected when the wounds occur in the vicinity of the diaphragm. However, such direct wounds are responsible for only 20% of the traumatic diaphragmatic hernias.

Indirect traumatic diaphragmatic hernia is one of the less apparent, but nevertheless more common and serious injuries, that has defied early diagnosis in approximately 70% of cases (1, 2). In this report of two cases which were recognized in time and managed in the acute phase, we will present the features that, hopefully, may lead to earlier clinical recognition and management of indirect diaphragmatic rupture.

CASE NO. 12

Hospital #436076.—A 32 year old white man was brought to the emergency de-

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partment of Elmhurst Hospital on November 3, 1967 following an automobile accident in which two other occupants of the vehicle were killed. He was sitting in the back seat of the car and was not wearing a seat belt. There was no loss of consciousness although the patient was confused and agitated. The chief complaint was pain in the left chest.

PHYSICAL EXAMINATION. The patient was in obvious respiratory distress. The vital signs were normal. There was an extensive avulsion type of laceration of the right frontotemporal scalp with a severe comminuted depressed fracture of the underlying bone. Function of the cranial nerves was undisturbed. The rib cage was intact. Auscultation of the lungs revealed an absence of breath sounds over the lower two-thirds of the left hemithorax where peristaltic sounds were audible. No signs of fracture of the extremities or pelvis were noted. Examination of the abdomen was unremarkable.

An immediate intravenous infusion was started, a nasogastric tube was inserted, and a Foley catheter was passed into the bladder. There was no blood in the urine. Coffee-ground material drained from the nasogastric tube. An abdominal paracentesis did not yield any blood or exudate. A complete blood count, hemoglobin and hematocrit determination were within normal limits.

X-RAYS. Skull studies revealed a severe depressed comminuted fracture of the right fronto-temporal region (Fig 1). Plain films of the abdomen showed no abnormality. Chest x-ray demonstrated a markedly elevated left hemidiaphragm with an underlying stomach gas shadow (Fig 2). The differential diagnosis between a traumatic hernia and eventration of the diaphragm could not be made with cer-



Case 12, Fig. 1. Radiograph showing comminuted fracture of right frontotemporal skull (Case 12).

tainty at this time. Gastrografin was introduced into the stomach via the nasogastric tube and revealed the abnormally high position of the stomach (Fig 3). In an attempt to outline the diaphragm and study its integrity 800 c.c. of air was injected into the peritoneal cavity. Since this maneuver did not demonstrate air under the diaphragm on x-ray, it was presumed that the air escaped into the pleural cavity through a rent in the diaphragm thus confirming the clinical impression of a traumatic diaphragmatic hernia.

COURSE. The patient was taken directly from the emergency department to the operating room. Immediately upon en-

tering the left pleural cavity via an 8th intercostal thoracotomy incision, a herniation of the stomach, transverse colon, small bowel and spleen was apparent (Fig 4). There was a long rent in the diaphragm which extended from an avulsion medially where the diaphragm was separated from its attachment to the costosternal angle and adjacent ribs. The laceration continued in an arcuate fashion over the dome and beyond with almost complete transection of the diaphragm. There was a second laceration, through which the cardia protruded, which began at the esophageal hiatus and extended transversely for 6 centimeters (Fig 5). The hiatal laceration was repaired with one layer of interrupted 00



Case 12, Fig. 2. Chest x-ray shows a mass of the left thorax with smooth upper margin and underlying gas shadow. Differential diagnosis between herniated stomach and eventration of an intact diaphragm cannot be made with certainty.

Mersilene mattress stitches. The abdomen was then explored through the larger laceration and failed to reveal any evidence of intraabdominal trauma except for a contusion of the anterior stomach wall. This explained the coffee-ground material which issued from the nasogastric tube. After replacing the herniated abdominal viscera, the large diaphragmatic defect was repaired in a similar manner up to the area of avulsion medially (Fig 6). The avulsed

gap was closed using pericostal 0 silk stitches which were passed through the torn diaphragm thus restoring the insertion of the diaphragm to the costosternal angle and rib cage. Following penicillin irrigation of the thorax, two chest tubes were inserted, one near the apex and the other at the base of the pleural cavity. They emerged through separate stab incisions laterally placed in the 9th intercostal space. The incision was closed in layers and the



Case 12, Fig. 3. Chest x-ray taken after introduction of gastrografin into stomach. Abnormally high position of stomach may be due to either hernia or eventration of diaphragm.

chest tubes were connected to an Emerson suction apparatus.

The patient was turned from the right lateral to the supine position. The neurosurgical team then debrided the depressed skull fracture and repaired the scalp wound. The operation was well tolerated and the postoperative course was uneventful. It was necessary for the patient to remain in the hospital for one month before all his confusion and agitation subsided.

CASE NO. 13

Hospital #437383.—A 24 year old white man was brought to the emergency de-

partment of Elmhurst Hospital on November 17, 1967, one hour after injury in an automobile accident. He was the driver of one of the vehicles and was wearing a lap type seat belt. There was no loss of consciousness. He complained of pain in the left hip area and over the left lower anterior rib cage.

PHYSICAL EXAMINATION. The left lower extremity was immobilized in a Thomas splint. No respiratory distress was noted. The pulse, respiration rate and blood pressure were within normal limits. Although external signs of trauma were absent, there was tenderness of the left lower rib cage. Auscultation of the left lower hemithorax



Case 12, Fig. 4. Operative photograph showing protrusion of stomach, greater omentum, transverse colon (upper arrow), small intestine, and spleen (lower arrow) from left thoracotomy wound.

disclosed the presence of peristaltic sounds but no breath sounds were heard. Left upper quadrant and suprapubic tenderness without muscle spasm were noted at the initial abdominal examination. There was marked tenderness of the left hip area which was also exhibited upon compression of the pelvis. During the examination the patient voided a bloody urine. Rectal examination revealed no displacement of the prostate gland.

An intravenous infusion was immediately started and blood was drawn for laboratory study and crossmatching. A nasogastric tube was passed into the stomach and drained normal gastric juice. A Foley catheter was passed without difficulty. An abdominal paracentesis was performed but no abnormal exudate or blood could be aspirated. The patient was then taken to the x-ray area of the emergency department accompanied by members of the surgical, urological and orthopedic staff.

X-RAY. Chest x-ray demonstrated a fracture of the 6th left rib posteriorly. There was marked elevation of the left hemi-

diaphragm with evidence of disruption at its central portion. There was a shift of the mediastinum toward the right; no gas shadows could be detected above the diaphragmatic level (Fig 7). Plain films of the abdomen showed no abnormalities. X-rays of the pelvis revealed multiple fractures of the left pubic rami as well as an impacted fracture of the left acetabulum and head of the left femur. An intravenous pyelogram indicated prompt bilateral normal urinary function of the kidneys and ureters with no extravasation. A cystogram demonstrated a displacement of the bladder towards the right side without any visible extravasation. This shift was believed to be caused by a large paravesical hematoma.

The abdominal findings rapidly and progressively increased to exhibit a generalized tenderness with muscle guarding. The white blood count was 30,000; however, the red blood count and hemoglobin were normal. The patient's condition remained stable. On the basis of the left upper quadrant and left chest findings, a high white blood count, and the x-ray abnormalities, a diagnosis of left ruptured diaphragm and probable ruptured spleen was made;



Case 12, Fig. 5. Operative photograph showing both lacerations of the left hemidiaphragm. Stomach leans on the apex of the larger laceration. Two fingers pass from the abdominal side through the second laceration into the pleural cavity.

in addition, there were the skeletal injuries already mentioned.

COURSE. The patient was taken directly from the emergency department to the operating room, where, under general anesthesia, the abdomen was entered via a left upper paramedian incision. Approximately one liter of blood was suctioned from the peritoneal cavity. An actively bleeding laceration of the lower medial surface of the spleen was encountered and a splenectomy was promptly performed. Further exploration revealed multiple contusions of the mesentery of the small bowel; herniation of the stomach into the left chest through a 12 centimeter laceration

of the diaphragm extending from the esophageal hiatus in an arcuate fashion to include the dome of the diaphragm; and a large retroperitoneal hematoma behind the sigmoid colon which extended around the bladder. The stomach was brought down into the abdomen and the diaphragm was repaired using interrupted 0 silk stitches followed by an inverting running 0 chromic layer (Fig 8). The retroperitoneal hematoma was not expanding and was left undisturbed. A gastrostomy was performed using a 22F Foley catheter. A chest drainage tube was inserted from the abdomen into the left pleural cavity through the esophageal hiatus. It was brought out of the abdomen through a



Case 12, Fig. 6. Operative photograph showing repair of lacerated diaphragm up to the area of avulsion. The remaining diaphragmatic edge will be held to the rib (arrow) with pericostal sutures.

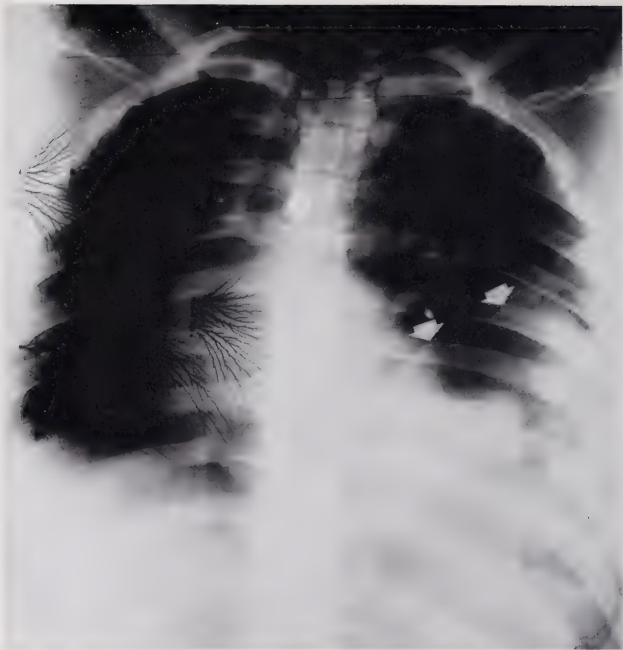
separate stab wound adjacent to the abdominal incision. Penrose drains were inserted into the splenic bed and similarly brought out through a stab wound in the left flank. Prior to the closure of the abdomen it was noted that the patient had a Meckel's diverticulum. This was excised and the defect in the ileum was closed transversely. After the wound was dressed and the chest tube was connected to an underwater system, the orthopedic surgeon passed a Steinman pin through the left tibial tuberosity to which traction was applied. The patient received 3000 cc of blood including the 500 cc administered in the emergency department. The opera-

tion was well tolerated and the patient was taken to the intensive care unit in satisfactory condition.

The subsequent postoperative course was benign. A chest roentgenogram demonstrated a lowering and a restoration of continuity of the left hemidiaphragm (Fig. 9). The patient was transferred to the orthopedic service for continued management of his skeletal injuries 13 days after his operation.

Pathogenesis

The diaphragm is constantly subjected to the stress of a difference in



Case 13, Fig. 7. Penetrating chest x-ray (Case 13) shows marked elevation of the left hemidiaphragm with evidence of disruption at its central portion (between arrows).

pressure between the thoracic and abdominal cavities. Any force of indirect trauma which increases this pleuroperitoneal pressure gradient tends to thrust the diaphragm upwards. Above the diaphragm the buffering effect of the lungs varies directly with the air contained within them; and the maintenance of this air pressure depends upon whether the glottis is opened or closed. Below the diaphragm, the large right lobe

of the liver and the right kidney act as protective buffers to stress against the right diaphragm; hence the low incidence of diaphragmatic rupture on the right side. The resistance to external trauma is weakest beneath the left hemidiaphragm. The part of the diaphragm subjected to the maximal force depends on the location and duration of the impact in relation to the position of the patient, thus explaining the various locations



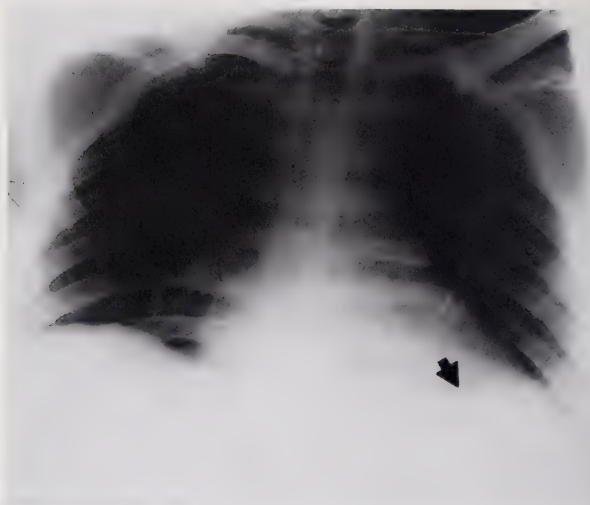
Case 13, Fig. 8. Operative photograph of repair of hiatal laceration, abdominal approach.

of diaphragmatic rents. The lacerations, usually arcuate, are most frequent at the central tendon and the congenitally weak posterolateral area. Disruptions at the sternocostal angle, as was noted in Case 12, are rare; lacerations extending through the esophageal hiatus, in both cases herein presented, are distinctly uncommon (2, 3, 4). We have not encountered mention of multiple lacerations such as were found in Case 12.

The overwhelming pleuroperitoneal pressure gradient explosively ruptures

the diaphragm at the point of minimal buffering resistance. If the tear is large, the viscera are immediately pushed into the pleural cavity abetted by the negative intrapleural pressure. If the rent is small, the natural pressure gradient favors an enlargement of the defect and a tendency for the viscera to wedge their way upward. The most frequent organs to herniate are the stomach, omentum, colon, small intestine and spleen, in various combinations (1).

Traumatic diaphragmatic hernia



Case 13, Fig. 9. Postoperative chest x-ray shows normal position and restoration of left hemidiaphragm.

occurs more commonly in men than in women; the incidence in children is low despite their many accidents and vigorous activities. This may possibly be ascribed to the increased resiliency and elasticity of the tissues at this age. Ninety-five percent of the herniations occur through the left diaphragm (5).

Surprisingly mild trauma, such as a voluntary twisting of the trunk, may occasionally cause diaphragmatic rupture. Usually, however, the patient is crushed by a weight, falls from a height, or is jackknifed in a vehicular accident. Frequent associated serious injuries are responsible for a worse prognosis than is found in the hernias

resulting from penetrating wounds. Fractures of the ribs, pelvis, lumbar spine and extremities are not uncommonly found (6).

Clinical Considerations

In the acute phase, the signs and symptoms are related to the misplaced abdominal viscera and their effects on the cardiorespiratory function. Once the hernia is established, suggestive symptoms are pain in the left lower thorax, in the left upper portion of the abdomen and in the left shoulder. A depression in the epigastrium and left upper quadrant of the abdomen, associated with paradoxical motion of this area, may be observed. The left

lower portion of the thorax may exhibit diminished respiratory excursion, dullness or tympany to percussion, diminished to absent breath sounds, borborygmus, and a shift of cardiac dullness to the right. In the presence of dyspnea and cyanosis, it may be extremely difficult to distinguish between a left-sided tension pneumothorax and a dilated stomach in the left pleural cavity.

The latent phase begins with the apparent recovery of the patient from the injury. It is one of variable length, months to many years, when the patient is relatively free from significant symptoms. There may be intermittent periods of colicky pain of limited duration in the epigastrium or left upper quadrant of the abdomen with radiation most commonly to the left lower portion of the thorax. A heavy meal often initiates or increases the distress. There may be aggravation of the pain when lying supine or on the left side. Tarry stools may be noted as a result of bleeding into the stomach, small intestine or colon secondary to vascular congestion. Compression of the cardiorespiratory system may produce dyspnea on exertion, palpitation, cough and hemoptysis.

In the obstructive phase, the aforementioned symptoms become increasingly severe. Nausea, vomiting and constipation herald the onset of an acute high or low intestinal obstruction depending on whether the stomach or colon, or both, are obstructed. If the stomach only is blocked, the abdomen may appear normal. The abdomen is usually distended in cases of colonic obstruction although it

may appear quite flat if most of the abdominal viscera are in the thorax. Strangulation with necrosis is not an infrequent occurrence (1, 7).

Radiographs

Penetrating views of the chest are preferable to bring out any abnormal shadows (2). Early in the acute phase no abnormalities may be noted. This should not deter the alert clinician from taking repeated radiographs in all cases of thoracoabdominal trauma or where any type of trauma is associated with abnormal clinical findings in the chest or abdomen. Such radiographs may subsequently reveal an unidentified shadow above the left hemidiaphragm. This may progress to a picture compatible with an abdominal viscus in the pleural cavity. Unfortunately, the nature of the abnormal shadow may remain obscure. Mediastinal shift associated with an elevated hemidiaphragm is strong circumstantial evidence of a possible ruptured diaphragm. The actual visualization of the discontinuity of the diaphragm is rarely seen or interpreted correctly (Fig 7).

The passage of a nasogastric tube may clarify an obscure finding if the tube can be seen in the stomach above the expected level of the hemidiaphragm. Yet, even in such cases, the arched shadow of the stomach wall above the gastric air bubble will resemble the hemidiaphragm and lead to an erroneous diagnosis of eventration of the diaphragm or gastric dilatation (Fig 2). A diagnostic pneumoperitoneum, if feasible, will usually outline and differentiate the diaphragm from the gastric wall.

On the right side, the x-ray appearances are altogether different. Herniation of the liver presents as a mass lesion simulating a tumor which might originate from the mediastinum, lung or diaphragm. The right lower hemithorax may be obscured by such a homogeneous density. Diagnostic pneumoperitoneum is apt to be most helpful in such cases.

If conditions permit, the use of contrast medium orally, by nasogastric tube, or per rectal administration, will usually delineate a herniated hollow viscus. If the radiopaque solution is held up at the cardioesophageal junction, it is likely that the stomach is herniated into the left pleural cavity producing an acute angle with obstruction at the cardia. If the contrast medium passes this angle, the herniated stomach will be visualized. When the solution passes on into the duodenum, the gastroesophageal and gastroduodenal junctions will be found to lie close to each other. The gastric position appears shifted with the greater curvature superiorly and the lesser curvature inferiorly. When there is no colonic obstruction, a barium enema will outline the herniated portion of the colon and positively establish the diagnosis. If there is occlusion of the colon by the edges of the diaphragmatic tear, the barium will stop below the splenic flexure, and the proximal transverse and ascending colon will usually be distended with gas. In cases of partial obstruction, some of the barium may pass the constriction and appear as several islands in the left pleural cavity.

Roentgenograms of the chest in the latent phase often cause confusion. A slight haziness or homogeneous den-

sity of the left chest are more suggestive of pleural effusion, inflammatory disease, or tumor, rather than a herniated abdominal viscus. Even air cysts and multiple fluid loculations may be interpreted as primary lung diseases. Atelectasis, pneumothorax, bronchogenic carcinoma, pneumonia and tuberculosis are some of the mistaken diagnoses which are made, based on erroneous interpretation of the plain x-ray of the chest. Radiographs using contrast media may be necessary to make the diagnosis sufficiently certain to warrant surgical treatment.

Therapy

Patients with acute diaphragmatic rupture commonly present the problems of multiple injuries. The handling of our cases has been described in some detail in order to illustrate our method of management of such patients. It is to be noted that all the necessary x-ray, resuscitation, diagnostic and therapeutic equipment is available for immediate use in the emergency area; the care is rendered by a medical team consisting of specialists in the various areas of injury; examination, monitoring of vital signs, passage of nasogastric or catheterization tubes, laboratory tests and diagnostic procedures are performed as simultaneously as is feasible; x-rays, or other procedures requiring movement of the patient, are supervised by a physician who remains with the patient; when urgent surgery is required, the patient is prepared and taken directly from the emergency department to the operating room. Operation was performed in our two cases within 2 hours after arrival of the patient.

Once the diagnosis of an acute ruptured diaphragm is made, operative repair is performed without undue delay. There are exceptions where the priority of diaphragmatic injuries is preempted in favor of control of hemorrhage, repair of a perforated viscus, or management of a severe compound fracture (Case 13). When the diaphragm cannot be repaired along with the correction of associated injuries, the operation for the reduction of the diaphragmatic hernia should not be delayed too long. A stabilized patient may rapidly develop serious cardiorespiratory insufficiency due to the pressure of the herniated viscera on the mediastinum. In cases of deterioration of the patient due to alarming mediastinal shift, a nasogastric tube may help considerably by decompression of the stomach. If the tube cannot enter the stomach, gastric aspiration through the chest wall with a needle is an accepted procedure provided the diagnosis is certain and the patient requires alleviation of the mediastinal shift in order to be operated upon immediately thereafter (8).

In the latent phase, surgical repair is recommended in order to avoid the complications of intestinal obstruction, strangulation, perforated gastric ulcers, bleeding acute ulcers, or hemorrhagic gastritis. Occasionally, a prohibitive surgical risk in an old patient with significant associated illness will preclude operative treatment.

In acute cases of diaphragmatic rupture the selection of abdominal or thoracic operative approach is frequently determined by the presence of concomitant injuries. Intraabdom-

inal hemorrhage or perforated viscus mandates an abdominal approach. Some surgeons favor this approach electively because they believe that it is less aggravating in a patient with severe skeletal injuries. It permits better exploration of all viscera, the right lobe of the liver, and both leaves of the diaphragm; there is less chance of overlooking retroperitoneal damage. Suture of the diaphragm is more difficult with an abdominal approach, especially when there is an avulsion from the rib cage or when the laceration involves the esophageal hiatus. In such cases a lateral extension to a vertical abdominal incision, or an extension across the costal margin into the pleural cavity, may be necessary.

In the latent repair of diaphragmatic lacerations the thoracic approach is favored by most authors (1, 2). It permits better control and liberation of adherent herniated viscera, complete expansion of the lung and technical ease in repairing any type or location of rupture of the diaphragm.

The repair of a diaphragmatic avulsion is a special problem. Reinforcing sutures around the ribs have been found useful and were employed in our case (9). The following other alternatives to avoid undue tension have been employed: attachment of the avulsed margin of the diaphragm to a higher intercostal space; a limited thoracoplasty of the lower ribs as required; crush of the phrenic nerve. In the restoration of a laceration involving the esophageal hiatus, the repair should be snug without pinching the esophagus. In this regard, we would avoid the passage of

a drainage tube through the repaired hiatus as was done in case 13.

Summary

Traumatic diaphragmatic ruptures are frequently overlooked in the acute phase because of a low index of suspicion, meager initial signs, and diversion of attention toward the management of concomitant serious injuries. This entity should be considered in all cases of multiple injury; particularly when there are fractures of the ribs, pelvis, or spine. The pathogenesis, diagnostic aids, and surgical treatment are discussed.

Two cases with multiple injuries and with special types of diaphragmatic rupture (avulsion, hiatal lacerations, multiple lacerations) are presented. Rapid diagnostic maneuvers and management by a surgical team of specialists were efficacious in effecting surgical repair within 2 hours after arrival at the hospital.

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CASE NO. 14

Gastric Perforation in a Newborn

Spontaneous perforation of the stomach is a life-threatening event which occasionally occurs in the newborn period. Early diagnosis followed by prompt surgical closure of the defect offers the only chance for survival (1, 2).

Although spontaneous gastric perforation in a neonate was first described by Von Siebold in 1826 (3), it was not until 1950 that Léger *et al.* (4) reported the first survival of an infant who was operated upon for this condition. In 1952, the first premature infant survived surgery for a gastric perforation (5). The entity is relatively uncommon, and although more than 150 cases have been reported (2), most have been isolated case reports; the largest single series consisted of 13 cases (6). In all cases combined, the overall mortality rate is 75% and the operative mortality 63% (2).

The following case is that of a premature infant who successfully underwent surgery for a spontaneous gastric perforation.

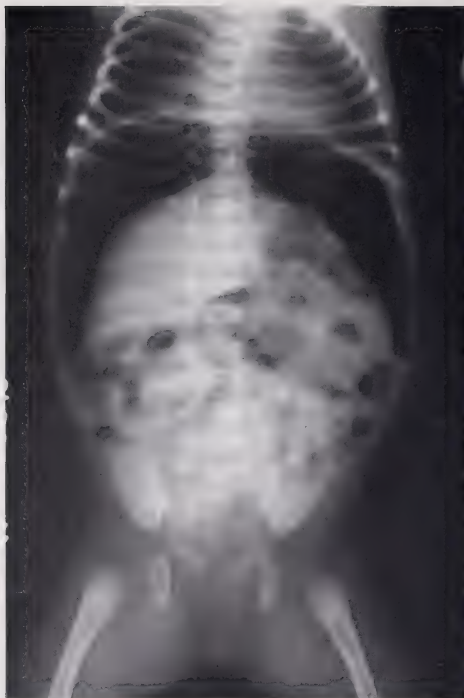


Case 14, Fig. 1. The infant at 40 hours of age showing markedly distended abdomen

Hospital #395606.—A normal 1960 gram (4 lb 5 oz) premature infant female was delivered spontaneously on November 4, 1966 following a 19-hour labor. Gestation was estimated to be 37 weeks. The mother was a 22-year-old para 5015. Demerol, 100 mg and phenergan, 85 mg were given three hours prior to delivery. The infant's Apgar score was 6; however, the child did not breathe spontaneously until three minutes after delivery. Oxygen was given by mask. Oropharyngeal suction was employed but no gastric suction was carried out. When the baby was transferred to the nursery her rectal temperature was 94°F. The temperature returned to normal over the following few hours. Physical examination on admission to the nursery revealed a well nourished, well developed, normal-appearing premature female infant. The first oral feeding of 10 cc of glucose water was given 12 hours after delivery. A subsequent feeding of 15 cc of glucose water was given three hours later and thereafter 30 cc of Similac was given every three

hours. The child had a normal meconium stool and voided. At 40 hours of age the infant vomited, and several hours later was noted to have abdominal distention and respiratory distress (Fig 1). At this time the patient's temperature was 99.6°F (axillary), the pulse rate 180 beats per minute, and the respiratory rate 68 per minute. The abdomen was markedly distended and tympanitic. Bowel sounds were absent. The Hgb was 22.5 gm/100 cc and the Hct 69%. The white blood cell count was 4,500/cu mm. The electrolytes and urinalysis were normal. X-ray films of the abdomen showed a large pneumoperitoneum (Fig 2). A saphenous vein cutdown was performed, a nasogastric tube was inserted and the patient was taken to the operating room.

Surgery was performed at 46 hours of age using endotracheal anesthesia. A large amount of free air and turbid fluid was present in the peritoneal cavity, and the abdominal viscera were covered by sheets of adherent curdled formula. A 4 cm



Case 14, Fig. 2. X-ray film of the abdomen taken in the upright position. A large pneumoperitoneum is evident.

longitudinal tear was found on the anterior wall of the fundus of the stomach, along the greater curvature (Fig 3). The ragged edges of the defect were excised and the perforation was closed in three layers. A Stamm gastrostomy was performed using a mushroom catheter. Saline was injected into the gastrostomy tube in order to distend the stomach and ascertain the security of the closure, as well as to detect any other leaks. No obstruction was found distal to the stomach. The

child did well postoperatively. Intravenous fluids, penicillin, kanamycin and salt poor albumin were given. Gastrostomy feedings were started on the sixth postoperative day. Oral feedings were begun on the tenth postoperative day. The gastrostomy tube was removed on the 17th postoperative day and the wound healed well. At 27 days of age the child vomited several times. X-ray examination of the abdomen showed some distention of the stomach but no other abnormalities were seen. The



Case 14, Fig. 3. Operative photograph. The stomach has been delivered into the wound. Note: A, the serosal surface of the anterior wall of the body of the stomach; and B, the gastric mucosa as seen through a 4 cm tear in the anterior gastric wall near the greater curvature of the fundus. Guide sutures have been placed at the edges of the defect.

infant was fed with glucose water, regurgitated occasionally but soon returned to regular feedings. An upper gastrointestinal series was performed prior to discharge and a normal, well-functioning upper gastrointestinal tract was seen. The child was discharged at 42 days of age weighing 2670 gm or 5 lb 14 oz (Fig 4). At the age of 2½ months she weighed 3550 gm (7 lbs 13 oz). There was no difficulty in feeding.

Histologic examination of the excised margin of the defect revealed only sub-

mucosal edema and hemorrhage. The muscularis propria was present.

Discussion

The etiology of spontaneous rupture of the stomach in the newborn is still not well understood. Prior to 1943 it was thought that acute or chronic peptic ulceration of the stomach was the basic disease which ultimately led to perforation (1). Al-



Case 14, Fig. 4. The infant prior to discharge.

though peptic ulceration occasionally does cause gastric perforation, it accounts for only a small percentage of the reported cases. In 1943 Herbut (7) suggested that rupture occurs through a portion of the stomach wall which is congenitally deficient in muscle fibers. This theory has been widely supported. Recently Shaw *et al* (8) presented evidence, based on experiments with puppies and examination of stillborn infants, to refute Herbut's theory. They concluded that congenital absence of gastric muscle has not been unequivocally demonstrated in any cases of spontaneous perforation of the neonatal stomach. Rather, potential weak points between interlacing muscle bundles are normal anatomical features of the wall of the stomach. Rupture may occur when there is distention sufficient to force apart the muscle bundles in one area of the stomach. The histological picture of muscle absence at the edge of the

perforation is a nonspecific finding; more likely a result of retraction of the muscle rather than evidence of agenesis.

Obstructions distal to the stomach due to atresia of the pylorus, duodenum or upper small bowel have been occasionally implicated as the cause of gastric perforations. Other explanations for gastric rupture have been trauma from feeding tubes, nasogastric tubes and suction catheters; distention of the stomach following resuscitation; septicemia; and anoxia (2). It has been reported that gastric perforations may occur in the adult after over-distention of the stomach with oxygen (9). It is of interest to note that the Kreiselman infant resuscitator, presently in use in many delivery rooms, will deliver oxygen at pressures up to 53 cm of water at the mask even though a water manometric blow-off system is supposed to limit the pressure to 15 cm of water (10). Intragastric

pressures of up to 80 mm Hg (109 cm of water) have been measured in newborn infants (11). This pressure was recorded in several infants with gastrostomy tubes who were given 2 to 3 ounces of oral feedings and then made to cry. Although specific causes for perforation have been documented in a few instances, the etiology of perforation in the majority of cases remains obscure.

In an effort to shed light on the etiology of spontaneous rupture of the stomach in the newborn, 12 cases treated at Elmhurst Hospital over the past ten years were reviewed (11). Factors considered were: maternal age, race, and parity; complications of pregnancy and delivery; type of delivery; infant's birth weight, sex, blood type, Apgar score, and body temperature; the use of oxygen and suction in the delivery room; and the type and volume of feedings. No correlations were found. However, certain consistencies in the development of symptoms and nature of the pathology were apparent. Most babies appeared normal at birth and were well for the first few days of life. Symptoms usually occurred on the third or fourth postnatal day. The first evidence of impending difficulty was usually a decreased intake of formula. Vomiting was not a constant feature but abdominal distention and respiratory distress were always present. The x-ray film was usually diagnostic and in most instances showed large amounts of free air.

Prompt surgery is the key to a successful outcome. Intravenous fluids, nasogastric suction, vitamin K, O₂ and antibiotics should be given

prior to surgery. If respiratory distress is severe, the insertion of a needle into the upper abdomen to allow the escape of intraperitoneal air may be lifesaving. Although perforations have been recorded in all portions of the stomach, the perforation occurred along the greater curvature of the stomach, usually anteriorly, in all 12 of our cases. Eleven of the twelve infants were operated upon, and six survived. Surgical treatment consists of laparotomy and location of the perforation or perforations, excision of the devitalized tissue at the margins of the defect and secure closure. A tube gastrostomy is employed. Prior to closing the abdominal wound the stomach is distended by the instillation of saline through the gastrostomy. This maneuver will demonstrate any unrecognized perforations and also tests the security of the suture line. Although rare, lesions distal to the stomach should be searched for. Postoperatively, gravity drainage through the gastrostomy and intravenous fluid administration are continued until bowel function returns. Gastrostomy feedings are gradually increased and then oral feedings are given.

Summary

1. A case of spontaneous perforation of the stomach in a premature newborn infant is described and a review of eleven additional cases is cited. 2. The various theories of the cause of this disease are discussed. The etiology remains obscure. 3. Prompt diagnosis and surgical closure of the perforation offers the only chance for survival.

A. Robert Beck

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CLINICO-PATHOLOGICAL CONFERENCE

Juvenile Diabetes Mellitus, Rheumatic Heart Disease, Fever, and Massive Hemoptysis

Edited by

FRANKLIN M. KLION, M.D.

A 12 year old Negro girl was admitted to The Mount Sinai Hospital with nausea, vomiting and Kussmaul breathing.

She was born in South Carolina (birth weight 3,330 grams), but had lived most of her life in New York City. She had developed normally and received the customary immunizations except for measles. Her past medical history was unremarkable. One of two living siblings has rheumatic heart disease, and there was no family history of diabetes.

Two and one half years earlier, at nine years of age, she was hospitalized at The Mount Sinai Hospital because of joint pains. The heart was slightly enlarged and a systolic murmur was heard at the left sternal border. The ASLO titer was 1:1250, and the erythrocyte sedimentation rate was 87 mm/hr. The patient responded well to bed rest, penicillin and steroid therapy. However, glycosuria and severe ketoacidosis subsequently developed and steroid therapy was discontinued. Her diabetes was initially controlled with a 2,000 calorie diet and 20-30 units of regular insulin daily. After two weeks of hospitalization she was maintained on 13 units of NPH insulin. Because of occasional shocklike episodes, insulin was temporarily discontinued. Two months later she was discharged on 3 units of NPH insulin daily. Prior to her final admission, the patient was hospitalized four times for diabetic acidosis, usually precipitated by minor infections. On each occasion the acidosis was treated with electrolyte solutions and insulin. At the time of her final admission she was receiving 60 units of NPH and 20 units of regular insulin daily. She had been placed on prophylactic penicillin for her rheumatic fever, but erythromycin was substituted because of allergic manifestations.

The patient was semiresponsive. The blood pressure was 120/80, respirations 40/min, Kussmaul in type, pulse 150/min, and temperature 97.2°F. Her pharynx and tympanic membranes were slightly reddened. Coarse breath sounds and rhonchi were heard bilaterally, harsher on the right than on the left. The heart was not enlarged to percussion but a Grade III holosystolic murmur, which did not radiate, was heard at the apex. The liver and spleen were not felt. The remainder of the physical examination was normal. X-ray examination of the chest taken during expiration showed prominent hilar markings on the right and an enlarged cardiac silhouette. The electrocardiogram revealed a sinus tachycardia. The hemoglobin was 12.4 mg%.

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TABLE I
Blood Chemistry

Day	Glucose (mg %)	CO ₂ (mEq/L)	BUN (mg %)	CL (mEq/L)	NA (mEq/L)	K (mEq/L)	ALSO	Serum acetone
1 1 a.m.	580	8.5		121	121	4		1± at 1:4
8 a.m.	230	11.5	10	102	127	3.5		
2 8 a.m.	570	18	12	98	142	5	1:166	
4 9 p.m.	380	21.4	18	86	125	5		
6 8 a.m.	510	24.5	13	99	136	5.2		
	459	25.5	6	100	139	4.7		

hematocrit 40%, white blood count 15,900 mm³ with 79% polymorphonuclears and 5% band forms. The ESR was 104 mm hr. The urine pH was 5 and the specific gravity 1.020. There was marked glucosuria and acetoneuria and a trace of protein. The serum albumin was 2.7 mg%, globulin 4.7 gm%, calcium 9.2 mg%, phosphorus 2.5 gm%, and alkaline phosphatase activity 14.5 King-Armstrong units. Latex fixation, heterophile agglutination test and an intermediate strength tuberculin test were negative. A tuberculin test (second strength) produced 5 mm of induration after two days. Three blood cultures were sterile. The results of other laboratory examinations are summarized in Table I.

She received 30 units of regular insulin i.v., and 30 units subcutaneously four times in the first 12 hours. In addition, the patient was given intravenous infusions of ionosol B. She continued to spill glucose, but the urine became free of acetone and she was maintained on 60 units of NPH and 20 units of regular insulin per day. Erythromycin, 250 mg, and aqueous procaine penicillin, 600,000 units i.m., were instituted because of a temperature elevation to 103.8°F, and the elevated white blood count. No untoward reaction developed. When *S. aureus* was isolated from her pharynx, staphicillin, 900 mg i.m. every six hours was added to the antibiotic regime.

The following day a nonproductive cough and chest pain developed. Flaring of the alae nasi and supraclavicular and suprasternal retractions were noted and rales were heard in the right lung. There was no evidence of congestive heart failure, although a hepatojugular reflux could be elicited. Five days after admission, the serum electrolytes were normal, her diabetes was well stabilized and her appetite was good. However, temperature elevations ranged from 102°F to 104.5°F, and the pulmonary findings were unchanged in spite of antibiotic therapy.

A roentgenogram performed three days after the initial examination showed no significant change. On the ninth day her temperature rose to 104.4°F and she was placed in an oxygen tent with mist. During the night she ceased breathing after bringing up large amounts of frothy red blood. Attempts at resuscitation were unsuccessful.

*Dr. Ralph Moloshok**: This 12 year old Negro girl was admitted to The

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Mount Sinai Hospital for the fifth time with diabetic ketoacidosis. The first admission to the hospital was two and a half years ago at the age of nine, when she had a typical history and findings of acute rheumatic fever. Her heart was slightly enlarged and she had a diastolic murmur at the left sternal border.

The antistreptolysin titer was elevated, and the sedimentation rate was rapid.

She responded well to bed rest and penicillin and steroid therapy. However, while on treatment, evidence of diabetes developed which increased in severity so that she eventually developed ketoacidosis and steroid therapy was discontinued. She was placed on 20 to 30 units of regular insulin daily, but as in most children with their initial episode of diabetes, her requirements of insulin dropped progressively, and she suffered shock-like episodes. She was eventually placed on a small dose of insulin and referred to the diabetes and cardiac clinics. She was rather difficult to control, partly due to poor cooperation, but many of the episodes of ketoacidosis were occasioned by minor infections.

On admission, she was semiresponsive, moderately dehydrated, and the respirations were rapid and Kussmaul in type. She had evidence of an upper respiratory infection. Her heart was not enlarged by percussion, and the Grade III holosystolic murmur and electrocardiogram were not changed from the previous hospitalization. A polymorphonuclear leucocytosis, and a rapid sedimentation rate were present, which continued throughout her hospital course. She remained in fair control throughout her hospitalization except for a rather persistent hyperglycemia and glycosuria. However, following rehydration and correction of the electrolyte imbalance, it became evident that she was febrile. Cultures of her nose and throat revealed a hemolytic *S. aureus* which was coagulase and mannitol positive, and it was felt that she probably had a staphylococcal pneumonia. In spite of appropriate therapy, she continued to run a persistently febrile course and the physical examination of her chest remained unchanged.

On the ninth hospital day she did not appear particularly to be any sicker than she was the previous day. Her cough was unproductive, but this is not particularly noteworthy in children.

The blood cultures were sterile. While the tuberculin test was weakly positive, I do not think tuberculosis was seriously considered. Her sudden death was completely unexpected. Possibly she had a massive pulmonary embolus or a necrotizing staphylococcal pneumonia which perforated into a vessel. Dr. Rabinowitz, would you present the x-ray findings?

*Dr. Rabinowitz**: The x-rays corroborate most of the clinical findings. When the patient had acute rheumatic fever there was generalized enlargement of the heart. The lungs were clear. Subsequent x-rays of the chest showed mild but generalized enlargement. An x-ray examination performed when she was having difficulty in breathing, showed marked elevation of

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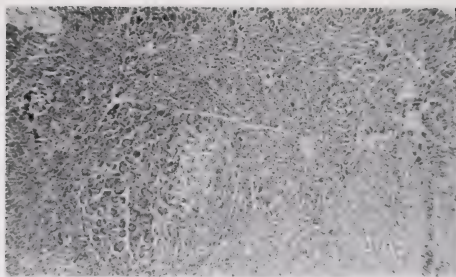


FIG. 1. Low power view of pancreas showing reduction in number and size of islets of Langerhans (hematoxylin and eosin).

the diaphragms. The heart was more enlarged, but this may have been due to the elevation of diaphragms. In addition there was fullness of both hila which could represent congested pulmonary vessels or superimposed lymphadenopathy. Three days later there was a definite infiltration in the right lower lobe and streaky infiltrations on the left side. The x-rays of the chest were consistent with a bronchopneumonia involving the adjacent lymph nodes. There was no evidence of fluid or abscess formation commonly seen with staphylococci.

In summary, she had cardiac enlargement, nonspecific in nature but probably attributed to rheumatic heart disease. Her present episode was a pneumonia in the right lower and left lower lobes associated with hilar lymphadenopathy.

*Dr. Strauss**: At autopsy, she was a slender Negro girl with pallor of the mucous membranes probably resulting from her terminal hemorrhage. The heart was slightly enlarged due to hypertrophy and dilatation of the left ventricle. The aortic valve showed minimal thickening of the cusps without deformity. The mitral ring was dilated, and the valve showed minimal thickening of the cusps and chordae, especially of the posterior leaflet with loss of the web-like insertion. A small McCallum patch was found in the posterior wall of the left atrium. There were no vegetations or verrucae on the valves. Histologically, there was vascularization and fibrous thickening of the mitral valve in addition to multiple perivascular fibrous scars in the myocardium of the left ventricle.

The exocrine pancreas was normal; however, pancreatic islets were reduced in number and size (Fig. 1). In sections stained with Gomori's aldehyde-fuchsin, few beta granules were observed, and these were mostly located at the periphery of the islets. Normally, beta cells make up about 60 to 90 percent of the islets. The loss of islet tissue was therefore attributed to

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loss of beta cells, and was not accompanied by fibrosis. Whether the reduction in the number of beta cells is due to a maturation arrest as has been suggested (1), or secondary to hyperglycemia (2), is still open to dispute. The latter concept has recently found increasing experimental support (3), and would be in keeping with observations in young diabetics who tend to have large islets during the early acute phase of diabetes with subsequent decrease of islet size in the more chronic forms (4).

The liver was moderately enlarged. Histological sections showed a diffuse fine cytoplasmic vacuolization of the liver cells, and numerous vacuolated nuclei especially in the peripheral zones of the liver lobules, due to the accumulation of large amounts of glycogen. This finding, which is not rare in young diabetics is attributed to excessive gluconeogenesis is not well understood. According to Vallance-Owen, it is due to the action of the pituitary, either directly, or mediated through the adrenal (5). In the process acetoacetic acid is formed at an excessive rate and leads to ketosis. This theory would explain the tendency to excessive hepatic glycogen storage in patients with brittle diabetes. In experimental diabetes, glycogenosis of the liver is not observed. A fat stain of the liver showed fat mainly in Kupffer cells. This may be related to her febrile illness rather than to her diabetes. The liver cells only contained very minute fat droplets close to the cell border facing the sinusoids, suggesting uptake from the blood stream by pinocytosis. The large numbers of polymorphonuclear leucocytes in the sinusoids reflected the peripheral leucocytosis.

The kidneys showed two alterations characteristically associated with juvenile diabetes. Neither was associated with clinical signs of renal disease. A tubular change known as Armani-Ebstein lesion consisted of glycogen in the loops of Henle. Today this is rarely encountered in diabetics who have been treated with insulin, and is probably an indication of glycosuria and not specific for diabetes mellitus. The other glomerular lesion represents an early manifestation of intercapillary glomerulosclerosis; it consists of deposition of basement membrane-like material in the mesangium of the glomerulus. It is found in patients with a short history of diabetes, with normal renal function, and may be found in prediabetic patients. Early lesions of this type are sometimes detected by electron microscopy, even before they are seen with the light microscope. In addition, there were multiple foci of interstitial inflammation probably a part of a generalized infection.

The spleen was soft and moderately enlarged, and an acute splenitis was seen microscopically.

No fluid was found in the pleural cavities, and most of the pleural surface was smooth and shiny. However, the posterior apical portion of the right lower lobe was dull and covered with a fibrinous exudate.

The lungs were voluminous and slightly heavier than normal. The peripheral portions of the lungs were ballooned due to emphysema, while the deeper portions were "rubbery." On sectioning, both lungs were red, granular and



FIG. 2. Abscess cavity in the right lower lobe, showing shaggy, necrotic wall. The arrow points to a broken-down lymph node at the hilus of this lobe.

finely mottled, due to fibrin and blood. The source of this blood was not apparent at the time of the autopsy, and a hemorrhagic pneumonia was considered most likely. However, histological examination revealed widespread aspiration of blood throughout the hyperacrated portions of the lungs, and many bronchi were flooded with blood and fibrin. There was a mild inflammation of the bronchial walls, particularly in the right lung. In the apical portion of the right lower lobe a cavity was encountered about the size of a plum (Fig. 2). Its wall was shaggy and necrotic, and surrounded by a rim of consolidated lung tissue. A communication between the cavity and a bronchus was not seen because the bronchial wall was completely destroyed. In the hilus, adjacent to the right lower lobe, there was a small sac-like structure which contained a semiliquid, white material (arrow, Fig. 2). Cultures from this material for bacteria and acid fast organisms were sterile. A microscopic section of a portion of the lung adjacent to the cavity showed a thickened pleura, with fibrinous exudate overlying the nonaerated lung tissue, and a large vessel entering the cavity. The vessel showed an organized occlusion and a mild arteritis. No organisms were found in the vessel, and evidently this was not the source of bleeding because it was completely occluded. We considered the possibility that the cavity may have resulted from a broken-down infarct which became secondarily infected, since the lung tissue adjacent to the cavity showed an organizing pneumonia. In the wall of the cavity there was also a small vein which showed early necrosis and incipient thrombosis. Necrotic exudate recovered from the cavity contained fungal hyphae.

The mucosa at the bifurcation of the trachea had a granular appearance, the walls were thickened, and the lymph nodes along the trachea were enlarged and matted together in a dense, inflammatory mass. A section of the trachea and the right main bronchus showed nonspecific, subacute inflammation. The epithelium was intact but infiltrated with plasma cells

and lymphocytes. Sectioning of the mass of lymph nodes disclosed multiple small abscess cavities within and between the nodes, containing many necrotic inflammatory cells and a few giant cells. In the exudate, broad branching hyphae were recognized (Fig. 3). Multinucleated giant cells contained fragments of fungi. Arteries and veins were involved in this lesion, with thrombosis, necrosis and inflammation. The inflammation extended into the left atrium, and into the right lower lobe. The child had no evidence of hematogenous dissemination or embolization, and no peripheral infarcts. The artery which supplied the apical portion of the right lower lobe was torn. At the site of rupture, the intima was lost and the wall was dull, granular and red-brown in color. Microscopic examination showed complete disruption of continuity of the artery and replacement by necrotic material (Fig. 4). The cartilage of a major bronchus close to the artery was also

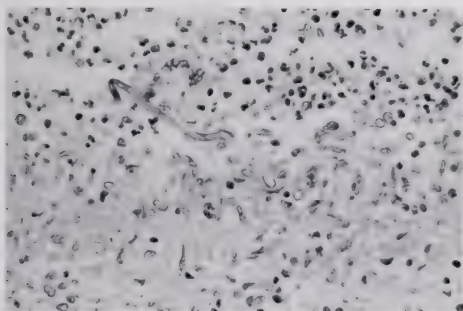


FIG. 3. Wall of parabrachial abscess showing purulent and granulomatous inflammation, and partially phagocytosed fungal hyphae in epithelioid and giant cells (hematoxylin and eosin).



FIG. 4. Right lower lobe branch of pulmonary artery showing necrosis and complete disruption of the wall (elastica-vanGieson).

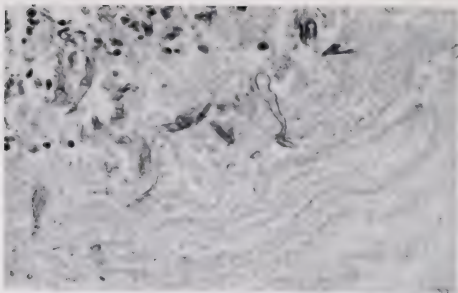


FIG. 5. Wall of necrotic pulmonary artery invaded by fungal hyphae (hematoxylin and eosin).

TABLE II
Phycomycetes

<i>Absidia corymbifera</i>	Fulminating infections, especially orbital, cerebral, pulmonary
<i>Mucor</i>	
<i>Rhizopus</i>	
<i>Mortierella</i>	Chronic skin ulcers
<i>Basidobolus ranarum</i>	Subcutaneous lesions (Africa, Indonesia)
<i>Entomophthora coronata</i>	Nasal polyps (horse)
<i>Hyphomyces destruens</i>	Subcutaneous lesions (horse)

necrotic. The arterial wall adjacent to the site of rupture showed acute inflammation, and in the devitalized portions of the artery were fungal hyphae (Fig. 5). We concluded that the fatal event was the rupture of a major branch of the pulmonary artery due to a mycotic pulmonary arteritis which led to fatal exsanguination and suffocation by aspiration of blood. Evidently, the patient was suffering from a fulminating, necrotizing, suppurative and granulomatous process involving the right lower lobe. The rapidly progressive character of the lesion was most likely ushered in by her most recent episode of ketosis. I cannot say with certainty whether she had this infection for some time in a more chronic form, although this is somewhat suggested by foci of granulomatous reaction and by the organizing pneumonia. On the other hand, it is possible that the mycotic infection was grafted onto a preexisting bacterial infection, partially controlled by antibiotics.

The organism consisted of broad, nonseptate, irregularly branching hyphae of variable length and thickness, having basophilic staining characteristics. On the basis of the histopathological characteristics, this fungus may be classed among the phycomycetes of which there are many species. Most are not pathogenic for man. In Table II are listed some of the species with

the sources from which they have been isolated. Italicized are those which may be associated with human disease in this part of the world. Although this form of mycosis has commonly been called mucormycosis, it may well be that the majority of visceral mycoses are caused by the species *Rhizopus*. A generic diagnosis can be made without isolation of the organism solely on the basis of the histopathological characteristics and the striking tendency to involve blood vessels. However, the various species can only be differentiated by means of isolation in culture which brings out characteristic differential features not present in tissues. For example, *Rhizopus* is characterized by a kind of root system, called rhizoids, connected by stolons from which the sporangiophores arise. These in turn carry the spore capsules or sporangia which release large numbers of spores. Sporangia develop only under aerobic conditions and have occasionally been encountered in pulmonary lesions.

Phycomycoses like other mycotic diseases have been recognized with increasing frequency. The fungus is known as *saprophyte* and has been isolated from soil, vegetable material, urine secretions and sputum. It becomes pathogenic only under altered conditions of host resistance. Nearly half of the known cases have been in patients with diabetic acidosis.

The phycomycoses produce a variety of clinical and pathologic syndromes, and I would like Dr. Moloshok to discuss the clinical aspects.

Dr. Moloshok: Mucormycosis, or phycomycosis, is probably the most acutely fatal infection in man. The disease was first reported in 1885. However, Gregory Haymaker and co-workers in 1943, were the first to report three patients with the so-called cerebro-ocular form. The infection rarely occurs as a primary disease in man, although it has been reported in dogs, cows, pigs, rabbits and other animals. Invariably it occurs secondary to some other preexisting condition. Almost half of the patients described in the literature were diabetic. The exact role of diabetes as a predisposing cause, particularly to the *Rhizopus* variety, is still subject to a great deal of debate. Whether diabetic ketoacidosis or glycosuria predisposes to superinfection is not settled. An environment high in sugar favors the growth of these organisms *in vitro*. However, most of the diabetic patients who acquire the infection also have ketoacidosis. Diabetes is not the only predisposing cause. Patients with leukemia or lymphoma, multiple myeloma, ulcerative colitis, following radiation therapy or steroid administration, also show an increased susceptibility. Many of the pediatric patients have debilitating diarrhea or fibrocystic disease of the pancreas.

In 1960, McBride collected 57 bona fide cases from the English literature and at present there are closer to 80 or 90 patients (6). We can divide the cases into subcategories which define clinical syndromes and may enable earlier diagnosis.

In the cerebro-ocular form, the fungus probably enters via the paranasal sinuses. The organisms invade and penetrate the bone tissue, causing ne-

erosis and a leucocytic inflammatory response. Characteristic of this type is the marked proclivity to invade vascular structures. The organisms invade the walls of arteries and produce the so-called mucor thrombosis. The infection spreads into the orbital area producing orbital cellulitis and ophthalmoplegia. Vascular thrombosis of the tympanic and carotid arteries, with invasion of the veins and lymphatics, produces a necrotic type of meningo-encephalitis which is usually fatal. Until 1960 only three patients with this syndrome have been diagnosed antemortem.

In the pulmonary form, the organism probably enters via the respiratory tract where it produces a lobar pneumonia. As in this patient, the fungus penetrates the bronchial walls and thrombosis of arteries and veins occurs with an ensuing infarction that may extend to the pleura.

The gastrointestinal form is seen most often in patients with primary intestinal disease but has been reported in patients with other debilitating diseases. Perforation of the stomach, the small and large bowel may occur rapidly or there may be mesenteric thrombosis with infarction and hemorrhage. If the fungus enters the circulation, widespread dissemination to various other organs can develop. Indeed, in the disseminated form, the portal of entry is usually through the gastrointestinal or pulmonary tract. The clinical picture is that of sepsis.

Diabetics primarily develop the cerebro-ocular form of this disease for reasons which are not apparent. The gastrointestinal form is uncommon in diabetics, whereas in patients with lymphomas, the pulmonary form of the disease is most common. A variety of predisposing conditions are found in patients with disseminated disease.

A diagnosis cannot be established by finding the organisms in the sputum or in other excreta because they are well known *saprophytes*. However, if the patient has a predisposing condition, there is good reason to suspect a pathogenic role. In a diabetic with an orbital cellulitis or a chronic unexplained sinusitis, it is incumbent on the physician to exclude mucormycosis. In the three patients who were diagnosed antemortem, the organisms were recovered from biopsy specimens or scrapings of the lesions. Biopsy of the lesion is easily performed because the area is anesthetic due to destruction of the innervation. In the 60 cases that I was able to review, the organism was cultured five times. In the other cases, the diagnosis was made at autopsy.

As in the present case, it is very difficult to assess the effect of therapy since the three patients who survived were treated by controlling the ketoacidosis and were also given iodides. One patient was treated with mycostatin.

In experimental animals, amphotericin B is effective and was also used in a recent case who survived.

Dr. Strauss: Are there any comments or questions?

Question: Is a special media required to culture the organism?

Dr. Moloshok: No.

Final Diagnoses: 1. PULMONARY PHYCOMYCOSIS WITH CAVITATION OF APICAL PORTION OF THE RIGHT LOWER LOBE. FIBRINOUS PLEURITIS. MYCOTIC ARTERITIS OF RIGHT LOWER LOBE BRANCH OF PULMONARY ARTERY, WITH RUPTURE INTO BRONCHUS. MASSIVE HEMOPTYSIS, AND BILATERAL ASPIRATION OF BLOOD. MYCOTIC BRONCHITIS AND PERIBRONCHITIS OF RIGHT MAIN AND LOWER LOBE BRONCHUS. SUPPURATIVE AND GRANULOMATOUS LYMPHADENITIS AND PERILYMPHADENITIS INVOLVING RIGHT PARATRACHEAL AND HILAR LYMPH NODES.

2. DIABETES MELLITUS. HEPATOMEGALY WITH EXCESSIVE ACCUMULATION OF GLYCOGEN. ARMANNI-EBSTEIN LESION OF KIDNEYS. DIABETIC GLOMERULOSCLEROSIS, MINIMAL.

3. RHEUMATIC CARDIOVALVULAR DISEASE, INACTIVE. MITRAL REGURGITATION. MCCALLUM LESION—LEFT ATRIUM.

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RADIOLOGICAL NOTES

CLAUDE BLOCH M.D. AND HARVEY M. PECK M.D., Co-Editors

CASE NO. 303

A 76 year old man complained of vague abdominal pains, but was essentially asymptomatic. There was no anorexia, change of bowel habits or rectal bleeding. Significant past history revealed a colonic resection for

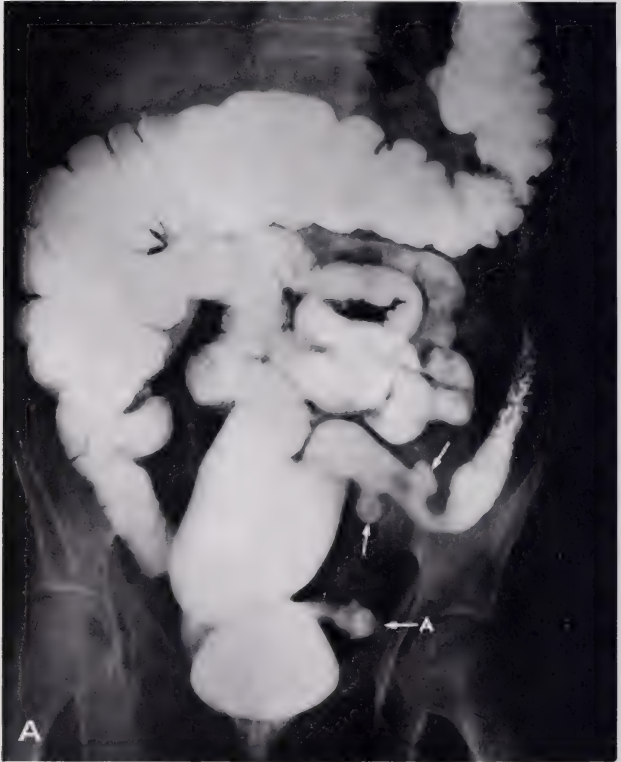


Fig. 1A.

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Case 303, Fig. 1B. The side-to-side sigmoid anastomosis becomes evident in an angled view of the sigmoid (between arrows). The proximal blind loop is identified below the barium-filled ileal loops (along upper arrows). The distal blind loop (arrow A) is now well demonstrated and its contours appear irregular and nodular especially inferiorly.

Case 303, Fig. 1A. Frontal view of the barium-filled colon reveals two pseudodiverticula within the proximal sigmoid (upper arrows). A barium-filled pouch-like structure is also noted to the left of the rectosigmoid (arrow A). Because of the retrograde filling of the ileum, the exact nature of this pararectal structure is not evident, especially since the sigmoid anastomosis is partially obscured by the overlying small bowel loops.



Case 303, Fig. 1C. Air contrast study of the distal blind loop of the side-to-side sigmoid anastomosis confirms the presence of nodularity and irregularity of its walls (arrows), as well as decreased distensibility of its mid-portion. No adjoining masses are noted.

a sigmoid carcinoma 25 years before. Physical and laboratory examinations were within normal limits. A routine barium enema revealed a side-to-side sigmoid to sigmoid anastomosis with two resulting blind loops. One blind loop was noted to point upwards, and represented the distal segment cul de sac. Another pouch-like pseudodiverticulum pointed laterally to the left side and was in continuity with the proximal portion of the sigmoid (Fig. 1A). The contours of the inferior blind loop were irregular and nodular with effacement of the normal mucosal pattern (Figs. 1B and 1C). Laparotomy was performed and the distal blind loop was identified; it was noted to be thickened but had a normal serosal surface. After immobilization, a simple stump resection was performed. No involved lymph nodes were found. Pathological examination revealed adenocarcinoma within the blind loop of the sigmoid. The patient had an uneventful recovery.

Discussion

This case illustrates the importance of routine barium enemas in patients with a previous colonic malignancy. Although anterior resections have replaced side-to-side sigmoid anastomoses in the treatment of carcinoma of the sigmoid, the present case represents a silent local recurrence in the pseudodiverticulum adjacent to the anastomosis. In this site, it did not produce any obstructive colonic symptoms. There appears to be increased

incidence of carcinomas within colonic blind loops, probably related to chronic stasis and low grade inflammation.

Case Report: CARCINOMA IN SIGMOID BLIND LOOP.

Acknowledgment

The editors wish to thank Dr. Gabriel P. Seley for permission to publish this case.

CASE NO. 304

An 82 year old woman was examined because of anemia. There had been no gastrointestinal symptoms, nor had the patient complained of abdominal pains or melena. The hemoglobin was as low as 10 gm%, with normocytic hypochromic characteristics. A preliminary film of the abdomen revealed a peculiar collection of gas in the right upper quadrant, which did not correspond to any normal bowel loop. Within this triangular structure, there appeared to be a small laminated calcific density (Fig. 1A). Gastrointestinal series revealed a normal stomach and duodenum. There was a side-to-side ileoileostomy situated in the right upper quadrant. A proximal dilated blind loop pouch was noted to correspond to the sac of gas identified in the preliminary radiograph (Fig. 1B). The calcified coprolith was now a smooth round filling defect within the lumen of the blind loop. The patient gave a history of an intestinal operation 25 years before for a benign small bowel tumor. She was treated with Vitamin B₁₂ and iron, and there was a prompt hemological response.

Discussion

The importance of a preliminary radiographic examination of the abdomen in performing gastroenterologic studies is well demonstrated in this case. The examination was primarily performed to rule out a bleeding point within the upper gastrointestinal tract to account for the anemia; however, the identification of the peculiar gas-filled structure in the right upper quadrant focused the examiner's attention to the small intestine and made it mandatory to continue the examination after a routine study of the esophagus and stomach. The entity of a postoperative small intestinal blind loop causing stasis and bacterial infection is now well known and amply described in the literature. It most commonly follows side-to-side anastomoses and often requires surgical correction, in addition to vitamin B₁₂ administration.

Case Report: SMALL BOWEL POSTOPERATIVE BLIND LOOP CAUSING ANEMIA.

Acknowledgment

The editors wish to thank Dr. S. T. Wild for permission to publish this case.



CASE NO. 305

A 64 year old man was seen in consultation because of severe constipation of eight weeks' duration. There had been no associated abdominal cramps, anorexia or weight loss. No rectal bleeding had been noted. The constipation became so severe that the patient required daily enemas for the previous week without much relief. Past history revealed an anterior resection eight years prior, for carcinoma of the sigmoid. Having noted some constipation starting about two years before, the patient received daily doses of Serutan for the previous 18 months. Physical examination revealed a mild hypertension and obesity. Slight abdominal distention was present without any tenderness or palpable masses. Hemogram and urinalysis were normal. Barium enema was performed. The sigmoid was shorter than usual, as seen after an anterior resection, but there was no evidence of recurrent disease within the sigmoid or pelvis. The left side of the colon and distal transverse colon were normally distensible with preservation of a normal haustral pattern. A mottled intraluminal filling defect, which had the appearance of inspissated material, filled the right colon up to the mid-transverse portion (Fig. 1A). There was constricting process or other colonic abnormality within the transverse colon. After evacuation, the left side of the colon emptied normally, whereas the barium outlying the inspissated material within the right side remained *in situ*. There was no evidence of proximal bowel dilatation (Fig. 1B). With a history of chronic ingestion of Serutan, which contains a great deal of cellulose products, a diagnosis of Serutan bezoar was made and the patient was given 3 ounces of Castor oil and tap water enemas. When barium enema was repeated it showed a normal colon with complete disappearance of the bezoar. (Fig. 2)

Case Report: COLONIC BEZOAR DUE TO SERUTAN.

Acknowledgment

The editors wish to thank Dr. Milton Singer, of Irvington N.J., and Dr. Marvin Bierenbaum, of Montclair, N.J., for permission to publish this case.

Case 304, Fig. 1A. Preliminary radiograph of the abdomen in the supine projection reveals a triangular collection of gas in the right upper quadrant (between arrows). The contours of this gas-filled viscus are smooth and no masses or nodularity are seen in association with it. A concentric faintly calcified density is seen within its center (arrow A). It has the appearance of a coprolith.

Case 304, Fig. 1B. During the course of a gastrointestinal series, the blind loop is now filled with barium (between arrows), and the filling defect is again identified (arrow A). The side-to-side ileoileostomy is noted under the pressure device.





Case 305, Fig. 2. After a course of laxatives and enemas, repeat barium enema reveals a normal colon, the intraluminal mass is no longer visible.

Case 305, Fig. 1A. Barium enema reveals a mottled density filling the entire right colon to the proximal portion of the transverse colon. This fills the lumen of the large intestine without disturbing its contours. Barium fills string-like interstices of the intraluminal filling defect without demonstrating any local colonic narrowing distally. The sigmoid is foreshortened (previous anterior resection).

Case, Fig. 1B. On the post-evacuation study, the left side and distal transverse colon are empty. On the other hand, the barium containing fibrous mass within the right side of the colon has remained unchanged from its appearance in Fig. 1A.

CASE NO. 306

A 75-year-old man complained of sudden onset of left upper quadrant pain. He was in good health until six months prior, when he was hospitalized for an acute myocardial infarction. He had an uneventful recovery and received long-term anticoagulant therapy. Physical examination revealed a mild hypertension. No petechiae or ecchymoses were noted on the skin or mucous membranes. There was moderate tenderness and guarding in the left upper quadrant as well as some left costovertebral sensitivity. No rebound tenderness could be elicited. There was a slight leukocytosis and the prothrombin time was 29/14 seconds. The anticoagulants were discontinued and an intravenous pyelogram and upper gastrointestinal examination were performed. The renal and psoas outlines were normal, and both kidneys functioned normally. The esophagus and stomach were also normal. A single short jejunal

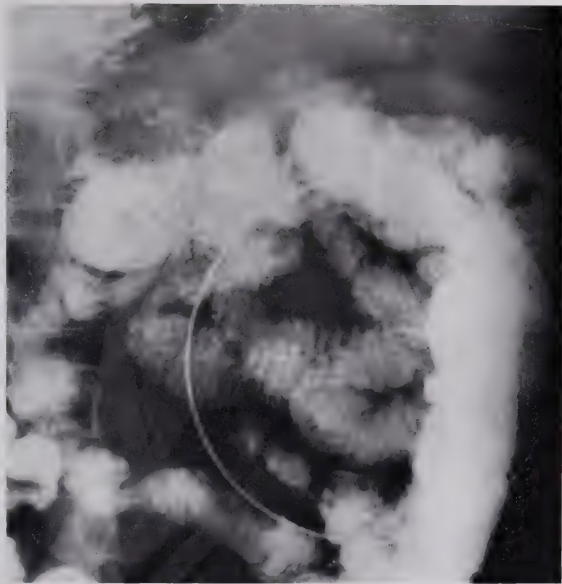


Case 306, Fig. 1. Pressure spot film during the progress of a gastrointestinal examination reveals a single short jejunal loop in the left upper quadrant to be slightly dilated and separated from adjoining small bowel segments. The valvulae conniventes were thickened in a regular fashion, but no ulceration or nodularity is identified.

loop in the left upper quadrant was noted to be slightly dilated and separated from the adjoining small bowel segments. The valvulae conniventes were thickened in a regular fashion, and the involved loop contained an increased amount of secretion (Fig. 1). There was no proximal dilatation or other signs of intestinal obstruction. No ulcerations or nodularity could be seen within the diseased jejunum. The remainder of the small intestine was entirely normal. Three weeks after this examination, repeat upper gastrointestinal series showed that the previously involved jejunal segment was now normal in every respect (Fig. 2). This corresponded to a total disappearance of the patient's clinical symptoms.

Discussion

This case is another example of reversible changes of submucosal hemorrhage in the small bowel after anticoagulant therapy. The findings of uniform thickening of the jejunal folds in a step-like fashion associated with some



Case 306, Fig. 2. Repeat examination of the same segment of jejunum three weeks after the discontinuance of anticoagulants reveals that the previously involved loop is now entirely normal.

dilatation, increased secretion and slight separation are characteristic (1). The involved loop does not present any increased irritability and there is usually no evidence of intestinal obstruction. When anticoagulants are discontinued and the hemorrhage stops, the affected small bowel usually returns to complete normalcy within a few weeks. If the local bleeding is more severe or prolonged, fibrosis and local stenosis may ensue.

Case report: JEJUNAL SUBMUCOSAL HEMORRHAGE FOLLOWING ANTICOAGULANT THERAPY

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In Memoriam

HOWARD L. GADBOYS, M.D.

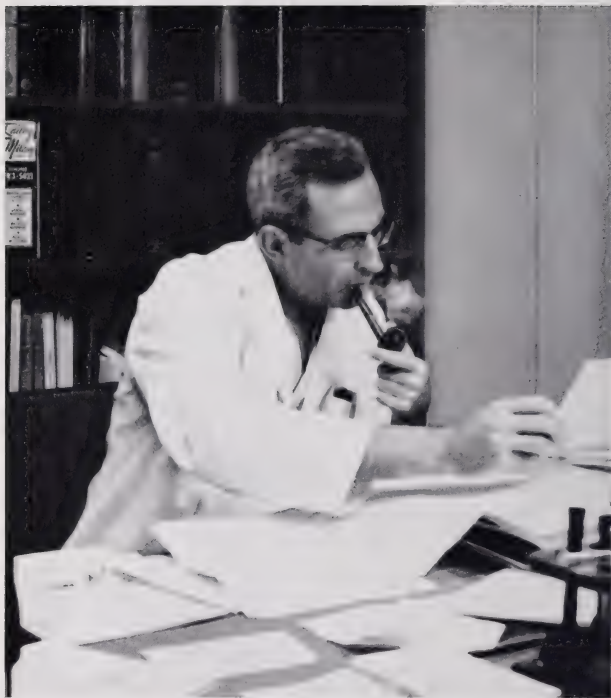
1923-1968

Howard Gadboys died suddenly on February 28, 1968 at the age of 44. With his death, The Mount Sinai Hospital and The Mount Sinai School of Medicine have both lost an inspiring and dedicated physician, educator and, investigator.

Doctor Gadboys was born in Waltham, Massachussets on December 6, 1923 and attended its public schools. He was graduated from Harvard College with an A.B. degree in 1945. After spending one year teaching zoology at the University of Massachussets, he began his medical studies in 1947 at the Boston University School of Medicine and received his doctorate from that institution four years later. His internship and general surgical training years were served on the Boston University Surgical Service of the Boston City Hospital, the latter period being temporarily interrupted by military service in the United States Air Force during the Korean conflict. Having developed a keen interest in cardiovascular physiology, Dr. Gadboys was naturally attracted to the burgeoning field of cardiovascular surgery and spent two years at the Presbyterian Hospital in Philadelphia working closely with one of the pioneers of cardiac surgery, Dr. Robert P. Glover. Upon completion of this work and wishing to be a *complete* thoracic surgeon, Howard spent a final year of training at the Albany Hospital under Doctors Allan Stranahan, Ralph Alley, and Harvey Kausel where he was exposed to a wide variety of non-cardiac thoracic problems.

In 1960, Dr. Gadboys joined the surgical faculty of the University of Miami School of Medicine first as an Instructor and, in the next year, an Assistant Professor of Surgery. It was here that he undertook to expand investigation of the adverse effects of homologous blood exchange in the experimental animal, work which had been initiated previously in collaboration with Doctors James W. Dow and James F. Dickson, III, in Philadelphia. It was subsequently shown that use of large volumes of homologous blood in man during whole body perfusion was also potentially deleterious. This work represents but one of a number of his significant contributions to the field of cardiac surgical physiology, all of which led to the reduced risk of cardiopulmonary bypass in present clinical open heart surgery.

He first came to The Mount Sinai Hospital in 1962 and served it with distinction as Associate Attending Surgeon for Cardiothoracic Surgery and Director of the Cardiothoracic Surgical Research Laboratory. His analytical approach to clinical problems was apparent to house staff and attending physicians alike and he quickly earned their admiration and respect both at the bed-



HOWARD L. GADBOYS, M.D.
1923-1968

side and in the operating room. His quick and at times sharp wit was his acknowledged hallmark and he lightened many a serious moment with *un mot d'esprit*.

Doctor Gadboys held the rank of Associate Professor of Surgery in the Mount Sinai School of Medicine. His abiding interest in medical education led to his appointment to the Curriculum Committee where he was influential in structuring an integrated educational environment which is intended to bring the student, basic scientist, and clinician into a continuing and ever broadening apposition. His efforts to bring a more quantitative dimension to medicine in general and surgery in particular led to the development of a Surgical Scientist program within the Department of Surgery and to his appointment as Chairman of the Training Subcommittee of the Bioengineering Committee of the School of Medicine. Doctor Gadboys' competence and effectiveness in this area was nationally recognized and for three years preceding his demise he served as a member of the Surgery Training Committee of the National Institute of General Medical Sciences, National Institutes of Health.

Howard Gadboys was a member of many scientific and medical societies including the Society of University Surgeons, the American College of Cardiology, the American College of Surgeons, the American Association for Thoracic Surgery, the Society of Thoracic Surgeons, the American Heart Association, the American College of Chest Physicians, the American Medical Association and its state and local affiliates, the American Association for the Advancement of Science, the New York Surgical Society, and The New York Academy of Sciences. He was certified by both The American Board of Surgery and The Board of Thoracic Surgery.

Doctor Gadboys is survived by his wife Wiltrud, two children, Jeffrey and Pamela, his mother, Mrs. Homer Gadboys, and one sister, Mrs. Beryl Downey. Acceptance of the fact that he has been taken is difficult. That he lives on in the hearts of his patients, students, colleagues, friends, and his family is indisputable.

ROBERT S. LITWAK, M.D.
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Current Trends in Curriculum Redesign*

HANS POPPER, M.D.

The curriculum of medical studies is at present in a state of flux. Within the last decade curricula have been revised in many medical schools in the United States; similar attempts, frequently far more extensive, may be found all over the world, particularly in new medical schools. Such radical revisions include those incorporated in the plans of the new medical school in Nottingham, England (1) or at the École de Médecine in Paris (2). In Germany, the new School at Ulm presents an ingenious wedding of medicine with the natural sciences (3). In Aix-la-Chapelle, a medical school is being created in a renowned technical university; here the emphasis falls on problems of bio-medical engineering. To these can be added new schemes in both old and new medical schools in the so-called developing countries.

Curriculum change is motivated by the new trends in medicine, *i.e.*, to develop physicians able to meet the needs of their society after completing post-doctoral training. The universal upheaval in social environment makes prediction of such needs, as well as of the future structure of society, most difficult. Even more hazardous are predictions of the status of medicine and its practice in the future, since these will vary in each country in accordance with social, economic, and scientific developments.

In spite of these patent difficulties, the first obligation of any group bearing responsibility for redesigning a medical school curriculum should be to *attempt* to predict a few of the specific needs of the society for which the medical student is to be prepared. Some trends in medicine apparent at this time are synergistic and facilitate revision; many more are antagonistic to each other and thus require a balanced evaluation of their significance against the background of local conditions.

The most challenging trend is the exponential growth of information relevant to medicine and useful in providing medical care. Since it is impossible for any one person to retain this mass of information, specialization becomes necessary and this usually occurs in the postdoctoral period. However, selection must be made of the material taught in the student years. This trend is, however, counteracted by several aspects of the developing unity of biology (4). One is the fact that biologic processes in lower organisms (for instance, viruses and bacteria) provide less complex models for studies with applicability to medical care; for example, the effect of antibiotics on protein synthesis can provide certain insights into the management of human disease; genetic principles or biochemical pathways in simpler organisms have implications for man.

Unity in biology also means that the borders between conventional sciences

From The Mount Sinai School of Medicine of the City University of New York, New York, N. Y.

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basic to medicine—biochemistry, physiology, pharmacology, and microbiology—which have hardened in the last century, are now disappearing since the same investigative tools are being used in all. Unity of biology will affect the departmental structure of the medical school and have impact on the type of experiments to be designed for the student laboratory. Most important, it offers principles which can be taught and which will replace facts which have to be memorized.

Another trend which follows the increase in relevant scientific information is the rapid change which occurs in such information. There is a growing awareness that the physician must be not only technically competent but a scholar all his life. He must be prepared to learn and utilize the new knowledge which will develop throughout his professional career. Even more difficult, he must be able to critically evaluate innovation. While this ability should be expected of a graduate of a school of higher learning, emphasis on scientific decision-making is, by tradition, greater in graduate schools which grant the Ph.D. degree than in the professional schools. Among the many useful devices which will help encourage the development of physicians capable of critical evaluation, contact with research, either for a limited exposure or as a lifelong avocation, ranks high.

Another trend felt universally but with varying expression is a greater concern for the feelings and dignity of the patient. In earlier times, this was an overriding consideration of the physician. The rapid development of biologic techniques in the last century with inherent therapeutic successes, both medical and surgical, led to greater emphasis on the technical aspects of medicine, and with this, the danger that the organ-oriented specialist may neglect emotional and psychological considerations.

The improvement in general education, however, has led to a "revolution of expectations" with the patient and his family often demanding more from medical science than it can deliver. Demands which center around the mental needs of the patient have brought consideration for many subclinical psychiatric disorders, including the natural anxiety associated with disease, but beyond that, for the dignity of man. Such consideration has been reinforced by recognition of the psychologic factors underlying organic disorders. While a conflict appears between the desire of the young physician for concentration on organ disorders and the demand of the patient and his family for overall care, this dilemma is a most important development in medicine and favors a return to the ideals of the great physicians of history as reflected in the humanists of the 18th century.

The patient-physician relationship is further complicated by the growth of specific, but potentially dangerous medical (pharmaceutical) and manipulative (surgical) procedures. This involves use of untested procedures which may not even carry great promise for the individual patient but are tried to gain experience not available through animal experimentation. Transplantation surgery and the application of anti-cancer drugs are examples of situations where such dilemmas occur.

The entrance of society itself into what was formerly a simple one-patient,

one-physician relationship is another trend which is steadily molding the future of medicine. The term "Community Medicine" embraces many areas which will be taught in the new curricula. The term, formerly applied to public health, has assumed different aspects today, as in the prediction of the risk of an individual in contracting disease by the detection of preclinical stages through screening methods. Another aspect is that of continued care for population groups, where comprehensive care of the family in periods of health, convalescence or in chronic disease has replaced the management of a single disease episode for one individual. A third, possibly the most potent factor, lies in the financial responsibility of third parties, governmental or private, for medical care. This is not the place for a discussion of schemes employed in various countries; we merely emphasize their potential impact on the curriculum.

A final trend involves the shortage of medical manpower. The rapid progress of medicine, the development of many effective, but time-consuming diagnostic and therapeutic procedures and, even more, the use of new and complex technological equipment greatly increases the need for persons trained in health sciences (5). While progress may be made in increasing both the number of physicians and the present type of medical technologists, it is unlikely that these increases will suffice to meet all the justified medical needs of the population in the future. It will be necessary to lengthen the arm, so to speak, of available physicians by transferring many responsibilities now carried out by the doctor to his assistants. Training of such auxiliary personnel must be thorough and specialized, but need not be as complex as that of the physician. Various plans are now emerging for training such clinical assistants; once-trained, they will probably become members of elaborate "health teams" comparable to those now existing in laboratories and industries and going far beyond the present transfer of certain responsibility from the physician, say, to the nurse. Since such paramedical personnel are being trained in the same institutions as the medical student, the latter can be alerted to his own part in the future health team. The medical curriculum should take cognizance of this still poorly-tested development which will also include education in the principles of logistics of patient care, and thus, in effect, represent an additional aspect of community medicine.

Six major trends summarized by such clichés as: 1) information explosion; 2) unity of biology; 3) continued ability of learning and decision-making; 4) human concern; 5) community medicine; 6) medical manpower shortage, must be enlarged by more specific trends of lesser overall impact, but of importance in curriculum design. These are:

A) The development of technologically complex equipment requires greater knowledge of physics, particularly electronics, mathematics, and chemistry. Most physicians in all fields will apply tools, the basic principles of which must be understood; this is particularly true in emergencies, for example, pacemaker failure. Computer and cybernetic principles play special roles; they will serve not only as time—and laborsaving devices in the organization of hos-

pital services, i.e. the scheduling of medication, supplies, nursing, and operating facilities, and for recording laboratory procedures, but as tools for information, as for instance where information collected on previous admissions can be readily retrieved for history-taking. Eventually, nationwide depots of such information (or at least those in organizations like unions) will aid in providing comprehensive medical care. Moreover, computer techniques are being applied in monitoring patients by integrating various clinical and laboratory features, e.g., in the postoperative period. Even greater influence on curriculum design will be the adoption of computer techniques in medical diagnosis. The interpretation of numerical data (laboratory findings, electrocardiographic and electroencephalographic tracings) is now technically possible. Clinical observations and pathologic findings, however, cannot be fully expressed in numerical terms for computer language, also, much clinical decision-making today is based on associations not even known to the physician. It is probably more important to teach, in today's curriculum, the limitations of computer techniques, for it is doubtful whether the psychological problems of clinical decision-making will be solved before the present generation of medical students have completed their professional careers.

B) The rapid improvement in secondary and college education, at least in the United States, brings students into the medical school who have already mastered much of the physical, chemical, mathematical, and computer background and, frequently, some of the biologic information which the medical school is presumed to provide (6).

This desirable development, however, creates one educational problem, that of unequally prepared classes and the necessity for "remedial" courses for equalization of preparation.

C) Teaching techniques are in a stage of flux (7). Tenets of psychology of education are being applied even at the university level; this is associated with objective measurement of correlations and evaluations. Even more significant has been the development of programmed teaching and utilization of teaching machines in part with the use of computers. While this permits the student to proceed at his own speed, he may become bored if he deals only with books or machines without personal contact with the teacher. While this development must be recognized in the modern curriculum, no one knows the future impact on medical education.

D) In the sciences basic to medicine, the scientific principles which have been accepted in the last 100 years have included precision of measurement and, more important, the philosophy of science and the logics of experimental design. The great biologic variations in human health and even greater in disease have made application of these principles difficult and have seduced the medical profession to engage in research guided more by impressions, often disguised as art, while the basic scientist has frequently looked on much of the work of his clinical colleague with contempt in spite of the rapid advances in medical care made in recent decades. Nevertheless, a clinical science is emerging which accepts the principles of basic science at the bedside; in fact, it is

required for the further success of medicine. The curriculum must reflect this development, but, at the same time, counteract the inherent danger of depersonalization.

E) The importance of bedside teaching introduced by Boerhaave in the 18th century (8) emphasized by its name instruction in hospitals where superior facilities were available and teaching material could be scheduled more effectively. Today many conditions can be managed in stages not requiring bedrest or hospitalization. The shift in teaching from bedside to outpatient clinic is increasing.

F) The population requiring medical care is constantly changing. The greater mobility of the population of the world demands of the physician some acquaintance with the habits and ethnic backgrounds of population groups which were previously confined to given geographic areas. Prolongation of the life span has emphasized the problems of older persons and increases the importance of the ineptly-designated "degenerative diseases." The improvement in medical care is making *partially* handicapped persons an increasing segment of the population which instead of being sheltered in chronic disease institutions, they have become useful and economically important members of society. Rural populations, too, are being reduced while urban dwellers with different medical needs are increasing.

G) Medical education beyond graduation is being continued in an organized fashion through different schemes—internships, residencies, and fellowships. Today the medical degree is usually only the intermediate step in formal medical education. Training in the "second portion of school years" after the formal degree must be considered in organizing the medical school curriculum.

H) Society through its regulatory arm, the government, is presently demanding the rapid utilization of scientific advances for the entire population irrespective of financial or geographic boundaries. This demand extends to the medical school and the medical scientific community and the sooner the student is informed of such demands, the better will be the social position of the physician in the future. It is certainly important that the future structure of medical care be directed by the physician and not by the sociologist.

The Basic Problem

As outlined, the medical school is presented with a challenge for the decades ahead. Increasing emphasis on quantitative biology must be introduced into medical care without losing bedside or clinical art. It will need to be tempered by human concern through the teaching of ethical and even the religious and behavioral aspects of man as a whole, while the problems and needs of the entire community and its ecology as expressed in material resources and social and cultural patterns must not be ignored (9). The conflict between the graduate school principle of continuing scholarship and the trade school requirements of firm, applicable knowledge necessary in medical care requires balance between flexibility and rigidity in curricula. The increase in relevant biologic and nonbiologic information and skills has led to a tendency

to postpone the time when the physician becomes a fully-trained practitioner—this produces financial hardship as well as the frustration of prolongation of the student years. Various plans for shortening the years of study have been proposed (6). In the United States, college years, usually four, are interposed between secondary and medical school education; attempts are being made to combine college and medical studies, reducing 8 years of study to 7 or even 6, by avoiding duplication of studies and eliminating certain areas, particularly technical courses in chemistry or physics which are presumably useless for the future physician.

Advantages accrue from the early introduction of the student to the simpler problems in medicine (for instance, anatomy during college years), and the presentation of cultural and philosophical subjects during medical school years. Results of several experiments of this kind are still unknown.

Another plan for shortening overall medical training brings consolidation of medical school studies with the postgraduate training, with the award of the degree of Doctor of Medicine perhaps delayed, as in Sweden. Internship as presently required in the United States would probably be deleted in such plans (10). Combination of medical and formal graduate education leading to the Doctor of Philosophy degree for the future medical scientist might bring forward the clinical scientist of the future if the student was not diverted, as he might well be, to a basic science irrelevant to medicine.

All of these schemes, greatly dependent on the geographic background, can be evaluated only after considerable experience has been accumulated. The key word of all these trends has become "integration" applied to a multiplicity of aspects.

Specific Devices

The only constant feature in curriculum design, to paraphrase another cliché, is change with experimentation. The design of the experiment is more difficult than most research problems. Just as sociological sciences encounter great difficulties in acquiring the logic and precision found in experiments in the natural sciences, the curriculum experiment is difficult to design, even more difficult to evaluate; this is true even when the experiment is short and does not extend beyond the life span of one generation. In a manner analogous to the sociologist who seeks to acquire the habits of the natural scientist, the curriculum planner is attempting to apply criteria borrowed from his biomedical research.

A few problems and devices are listed below without evaluation of merits, since the design of an individual school must depend upon financial and other geographically determined circumstances. The list is by no means complete and solution of any one problem is bound to raise new questions.

1) The amount of total teaching time in educational institutions is being increased by reducing long vacation periods during summer months, at holidays and between semesters. These periods were formerly considered necessary both for recreation and, in many instances, to permit the student to earn

sufficient money to finance further study. The periods were also used for travel, for paid service in a medical establishment, or for elective studies in the same or other school, with varying degrees of supervision.

The increase in the volume of course content has led, in many institutions, to a drastic reduction of periods for recreation (to as little as two weeks). It appears sound to provide either long summer vacations of two to three months' duration which permit organized activity of elective character or have very short vacations if financial considerations permit.

2) The selection of curriculum subject matter entails identification of the minimal amount of information in each discipline relevant to medicine (9). In view of the limited time available and the natural desire of instructors in each discipline to offer as much as possible to the student, a balanced compromise must be developed. This should not reflect the local power and personal eloquence of the representative of a given field.

There is a trend toward reducing morphologic data in favor of functional considerations. This has led to an increasing teaching load in biochemistry during the first years of medical study, with a progressive reduction of instruction in anatomy, particularly gross dissection, where more emphasis is given to the viscera than to the extremities. The emphasis upon principles rather than on facts enters here; in the practice of medicine, however, the knowledge of a body of facts is required which might not necessarily be explainable by known principles. The time allotted for behavioural and social sciences is now being increased in most institutions.

3) A major problem is the selection of teaching methods. The formal lecture to large student groups which was the main device for presentation in past decades, is now being degraded because of the barrier it places between teacher and student. The lecture is still useful, particularly in the first years of study, for imparting the initial "dictionary" of a discipline. Moreover, occasional exposure of the student to dynamic teachers is a valuable experience. For the lecture to be effective it should never be repeated but completely reorganized annually.

Teaching in small groups, both in the preclinical and clinical years, ensures a close interchange between student and teacher. This is particularly true when seminar techniques enforce active student participation. When course material is prepared in advance a student may become teacher in a given session and this usually results in greater enthusiasm on the part of students. The seminar facilitates the spotting of deficiencies in the instruction of the group, namely, extremes of boredom or of lack of understanding. The weaknesses of single students so located can often be corrected before frustration brings failure or dropout. The ultimate in teaching methods is the one-to-one tutorial system on which the great tradition of Oxford is still based.

The apprenticeship principle is, if possible, a valuable supplement to other teaching methods. A useful device is an enlargement of the student advisor system. Whether a student thesis based on personal research or library work is useful in the medical school has not been decided. The utilization of audio-visual aids, models, and teaching machines has not yet been evaluated.

4) The quandary of choice between "trade" and graduate school is reflected by the way time is usually allotted to the rigid core curriculum taken by all students and the free curriculum or elective periods during which the student is permitted to study one area in depth by working in a laboratory, clinic or a social area, usually on a tutorial basis. He may even spend this time in an affiliated university on a nonmedical subject.

The amount of time devoted to the core curriculum is closely related to the body of information and skill considered indispensable for the student who is granted the degree of Doctor of Medicine. At present the amount is not established. Both content and teaching time of the core curriculum vary widely, ranging from semesters or trimesters where no elective courses are permitted, to periods in which the elective or free curriculum exceeds one-half the total teaching time.

We should separate elective time from free time; the student is entitled to use the latter for relaxation or for study and meditation. Elective periods may be of several kinds; short seminars, courses from which the student may select one or more, long periods of study in depth in one area extending over many months. The core curriculum may parallel the free, *e.g.*, instruction in one, mornings, in the other, afternoons. This appears a preferable plan in pre-clinical years, while it seems better to assign block time to electives during clinical years. Another device in operation concentrates preclinical and clinical core curriculum in the first two years of study, and allows elective activities in both areas during the later years (11).

Elective periods require careful planning and supervision even when the student becomes a close and useful co-worker to his tutor in daily activities in the laboratory or at the bedside; this requires great expenditure of effort on the part of faculty members.

Elective time can include cooperative or independent research on the part of the student and, at the very least, it should permit opportunity for independent thought. The sharpening of intellectual ability and future habits which derive from exposure to research must be weighed against the student's own interest and available time.

The exposure in depth to one area is in keeping with the prevailing trend of early testing of the student's abilities and motivation. It should enable the student to make an early career decision as to whether he wishes to devote himself to medical, surgical, laboratory, behavioral or social (community medicine) activities. While some students require many years of maturation to come to a firm decision, others very early detect their basic area of interest. Many schools now attempt to encourage an early choice of careers. Another aspect of this testing may be the decision of a student to devote himself to a basic science relevant to medicine and to obtain the Doctor of Philosophy degree. The need of society for paramedical scientists is going to be at least as great as that for physicians. It is essential to spot potential candidates without considering them "dropouts" from medical schools.

5) The problem of integration of teaching (12) has various aspects: One concerns the simultaneous presentation of identical material from many view-

points independently of the respective disciplines in contrast to the assignment of block time to a given discipline; the material may involve preclinical subjects—anatomy, biochemistry, pathology—or clinical, such as internal medicine or surgery. In preclinical years this would include combined presentation of the normal and abnormal aspects of an organ system, *e.g.*, blood or the cardiovascular system, or of biologic processes, such as growth and development, or of response to injury, described simultaneously by biochemists, anatomists, physiologists or geneticists *et al*, in some instances in combined sessions. Even with separate sessions, close coordination, usually through a multidisciplinary program committee, is required to cover the entire area without duplication. Thus, normal anatomy and histology would be taught at the same time as biochemistry, pharmacology, physiology, and pathology of a given subject area.

Integrated subject teaching, in contrast to block teaching, requires a large faculty and great expenditure of teaching time. Integration in the preclinical years is widely applied at present in the United States. Attempts are also being made to extend this plan to clinical instruction—to teach simultaneously medical, surgical, and pediatric aspects of an organ group, *e.g.* cardiovascular, gastrointestinal, musculoskeletal diseases. Whether this is effective is not yet established. In the teaching of surgical aspects diagnostic rather than technical (operative) problems are emphasized. An extreme example of such plans would be the full integration of preclinical with clinical teaching, at the same time including the social and cultural aspects. In some ways, this would be a return to the teaching methods of earlier centuries.

The integration of clinical material into the basic science years is a relatively simple matter, as when, for instance, patients are presented to illustrate the basic problem under discussion, *i.e.*, diabetes. It is far more difficult to recall basic science information during the clinical years, and various devices are being used to interest the student in basic sciences in his clinical experiences. One of the most effective means can probably be built around clinical pharmacology which permits the reintroduction of many basic science problems.

Integration of subject matter must be distinguished from integration at the level of the teacher. Here, for instance, the pathologist may instruct in normal histology, the surgeon or radiologist may teach gross anatomy, the ophthalmologist may present some aspects of physiology, the clinician deals with pharmacology. This would be true to the principle that the teacher should only present areas of major interest to him. Gross anatomy may not be an area of research interest for the surgical specialist but he will be concerned with it in his daily activities.

Integration attempts may lead to reorganization of school departments. Several departments dealing with basic sciences may be combined into a single department of biology, with subdivisions covering physical, chemical, and morphologic aspects. Departments of neuroscience have already been established. On the clinical level, integration is facilitated not only by specialized clinical units, but particularly, by existence of clinical research centers dealing

with one group of diseases, or, at the least, intensive care units devoted to one type of disorder.

6) Another aspect of integration lies in the teaching area reflected in the concept of multidisciplinary laboratories which serve as a "home base" for the student (13). These offer several advantages: (a) The laboratory gives the student a place in the school which belongs to him for instruction, laboratory work and study and represents an important factor in his morale. Teachers come to the student instead of the student wandering from lecture to lecture. (b) It saves space, since laboratories for several disciplines can be combined. (c) It permits the organization of multidisciplinary experiments.

Laboratory exercises are frequently criticized today. They are essential in the study of morphologic facts which are easy to present under laboratory conditions and are not readily learned without them. The teaching value of chemical, serologic or quantitative hematologic exercises can, however, be challenged. In multidisciplinary laboratories, more sophisticated problems can be selected to which several techniques can be applied, in which the result need not necessarily be predicted. This would replace the simple "cookbook" experiments now commonly carried out with experiments enhancing understanding of problems. The value of teaching simple urinalysis and blood counts is questioned today, since most of these techniques will be carried out by automated equipment, obviously depending on local circumstances.

Architectural planning of these multidisciplinary laboratories is also related to the curriculum. They should serve as seminar and lecture rooms at least for smaller groups, accommodate benches for exercises requiring sitting or standing, provide attachments for teaching machines, as well as desks for study. Devices are being developed for the storage of bodies so that even gross anatomic dissection can be carried out there.

7) Many curricula allow for the early contact of student and patient, thus giving the study of basic science relevance to medicine and enhancing the motivation of the student who has chosen to become a physician. Previously this student would not see patients until later in his studies. Early patient contact may also provide opportunities to introduce social, behavioral, ethical, ethnic, and economic aspects of medicine; such problems in individual patients can be brought to the attention of the student early without expecting much medical knowledge on his part, *e.g.* when he sees patients in the outpatient clinic or hospital. Gradually the skills of history-taking and physical examination are introduced, the student learns prescription and order writing and simple techniques like drawing blood. In some schools, the student is assigned a family early, for instance, one with a pregnant mother, which he follows closely through the events of pregnancy, labor, and infancy. In other schools, he deals with family groups burdened by both chronic and acute disease, which gives him an early understanding of comprehensive medicine. Another device is a structured course of introduction to clinical medicine starting immediately on entrance of the student into medical school. It may expose him to personal, community, and clinical problems of individual pa-

tients with rising sophistication as the student acquires knowledge and experience. Moreover, it can be dovetailed with the biologic instruction to illustrate the relevance of the basic science information taught at a given period to one patient. All these devices serve to prepare the student emotionally and intellectually for the study of patients in his clinical years, counteract depersonalization and also protect the student from excessive identification with the patient's problems. Otherwise, introduction of social, humanistic, and cultural problems into the medical curriculum remains a difficult step for the student mainly engrossed with those of a biomedical nature.

8) For the introduction of physical sciences, including biomedical engineering, into the curriculum, a satisfying solution still has to be developed.

While many schemes have been presented, it must be emphasized that the most important ingredients for success in medical education are: 1) The enthusiasm of the faculty for teaching, regardless of the curriculum; and 2) The ability of the student to integrate the material offered. Let us also remember that the best students will learn effectively with any curriculum, the worst, with none. Therefore, the type of curriculum is crucial only for the middle group and we do not know how large this group is.

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Contralateral Trigeminal Neuralgia in Meningiomas of the Cerebellopontine Angle

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Ipsilateral trigeminal neuralgia has often been reported in neoplasms of the posterior fossa. Tumors such as acoustic neuromas, meningiomas, and cholesteatomas have frequently been responsible, while rarer tumors have also been reported as the cause of pain in the trigeminal distribution. Other conditions such as arteriovenous malformations, arterial loops, angiomas, congenital anomalies, and adhesions have occasionally been implicated.

Contralateral trigeminal neuralgia, however, has been reported only infrequently in relation to tumors of the posterior fossa. This possibility was first emphasized in the literature by Hamby (1). He presented two cases of meningioma, one of the cerebellopontine angle and one of a cerebellar hemisphere, both of which caused severe contralateral *tic douloureux*. In his discussion, Hamby pointed out that one cannot assume that the character of trigeminal neuralgia is sufficient to distinguish it from pain due to organic lesions of the trigeminal pathways or that organic lesions physically disturbing the trigeminal pathways always cause sensory changes. The second case of Parker, a patient with an acoustic nerve tumor, was cited (2). In this case, right trigeminal neuralgia without sensory change of the face was severe. Alcohol injection of the second and third divisions of the trigeminal nerve brought relief from the facial pain. Other signs such as left-sided deafness, nystagmus and ataxia led to an exploration and partial removal of a left cerebellopontine angle neurinoma. Autopsy revealed that there was marked distortion of the brain stem, so that the pons and the medulla were pushed far to the right of the midline and that compression of the right side of the pons against the petrous portion of the temporal bone had taken place.

Subsequently, other cases have been reported in the literature. Roger and associates successfully operated upon a patient with neurinoma of the right cerebellopontine angle who initially suffered attacks of left facial pain involving all three branches of the trigeminal nerve (3). Examination revealed left-sided hypesthesia of the mucous membranes of the gums and tongue. There was abolition of the left corneal reflex and very slight hypotonia of the left side of the face. Papilledema and right hypacusia were present. A crossbow incision was carried out and exploration of the right cerebellopontine angle was positive after a negative exploration of the left angle. The patient recovered rapidly and was free from trigeminal attacks. Right hypacusia and right facial hypesthesia remained.

Petit-Dutaillis and associates reported a case of meningioma of the right cerebellopontine angle which caused initial right trigeminal anesthesia but

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later caused severe *left* facial pain in the ophthalmic division (4). The only objective signs were corneal hypesthesia and bilateral pharyngeal hypesthesia. Caloric tests were not carried out. Petit-Dutaillis and Daum reported another case of meningioma of the lateral recess which caused contralateral trigeminal neuralgia unrelieved by several direct operative interventions (5). There was another interesting case of trigeminal neuralgia, occurring in the second and third division of the left side three years following removal of a meningioma from the convexity of the right cerebellar hemisphere, which was described by Rodriguez-Arias (6). The patient also suffered intermittent bouts of intracranial hypertension. Three episodes of *tic douloureux* were relieved by intravenous procaine.

Review of the literature to date reveals only these seven cases of contralateral trigeminal neuralgia. Two of these cases were acoustic nerve tumors and five were meningiomas. Of the latter, three were meningiomas of the lateral recess or cerebellopontine angle and two were meningiomas involving other portions of the cerebellum.

We present two additional cases of meningioma of the cerebellopontine angle with contralateral facial pain. The phenomenon and significance of contralateral trigeminal neuralgia are discussed. In addition, cases from the literature with contralateral trigeminal hypesthesia and/or contralateral involvement of the acoustic nerve are discussed. Formulations of the pathophysiology involved are summarized.

Case Reports

CASE I. A 48 year old woman was admitted to the hospital in 1959 for evaluation of right hemiparesis and progressive gait disturbance of 15 years' duration. Dysphagia, dysarthria, and visual complaints were more recent symptoms. From 1950 on, the patient complained of sharp, lancinating left facial pain in the first and second divisions of the trigeminal nerve. The pain was aggravated by swallowing. It had increased in severity up to 1955 and narcotics were required for relief.

The neurological examination in 1955 revealed horizontal and vertical nystagmus, diminished corneal reflexes bilaterally, right lower facial weakness, diminished right caloric response, and diminished pharyngeal reflexes bilaterally. The patient was unable to walk without support. Right-sided spasticity, hyperreflexia, bilateral Babinski signs, and left-sided ataxia were noted. Hearing and sensation were intact. Lumbar puncture revealed an opening pressure of 230 mm of water; the cerebrospinal fluid protein was 350 mg%. The patient received eleven infusions of stilbamidine with temporary relief of pain. The neurological examination four years later revealed, in addition to the above findings, a mild organic mental syndrome, bilateral facial hypalgesia, right-sided hearing loss, limitation of upward gaze, and defective optokinetic nystagmus.

Skull films showed no abnormality of the petrous pyramids. The pneumoencephalogram demonstrated the fourth ventricle to be deviated backward and to the left. The cerebellopontine angle cisterns did not fill with air. The vertebral arteriogram in the frontal projection showed a moderate upward and medial displacement of the first part of the right superior cerebellar artery. The basilar artery described an arcuate course toward the left. In the lateral view there was elevation of the first part of the superior cerebellar artery.

At operation a large, encapsulated tumor was found in the right cerebellopontine angle. The tumor extended through the notch of the tentorium cerebelli. Autopsy revealed it to be a meningioma which arose from the dura overlying the petrous apex. The tumor filled

the right side of the posterior fossa and projected into the middle fossa. The mass embedded itself into the right lateral aspect of the brain stem causing severe compression, distortion, and medial displacement, greatest at the level of the pons. There were fresh hemorrhages in the tegmentum and base of the right side of the pons and in the lateral aspect of the right cerebral hemisphere.

CASE II. A 57 year old woman was admitted to the hospital for the first time in 1960 because of inability to maintain her balance. Five years prior to admission the patient complained of pain on the top of her head. Three years prior to admission she reported pain on the *left* side of the face of a burning quality. Left orbital pain was also present. Two years prior to admission she noted decreased hearing in the right ear; tinnitus was greatest in the left ear. Impairment of control of her right foot was noted. Six months prior to admission the right side of her face became numb. Swallowing difficulty and nasal regurgitation followed.

The neurological examination revealed the patient to be oriented and alert. The gait was wide-based and staggering and she fell to either side. The Romberg test was positive; she fell to the right. There was transient nystagmus on right lateral gaze and sustained fine nystagmus on left lateral gaze which was increased on head extension. The right corneal reflex was absent; there was diminished sensation to pin prick on the right side of the face and tongue. Hearing was decreased in the right ear. There was no facial weakness. The soft palate moved well but the pharyngeal reflex was diminished. The patient showed slight tremor on finger-nose testing; heel-knee testing was slower on the left. The biceps reflexes were brisk; there were bilateral Babinski signs. Caloric tests revealed an absent response on the right; the response on the left was normal.

Skull films and tomograms through the petrous bones were unremarkable. The pneumoencephalogram showed symmetrical dilatation of both lateral and third ventricles. The aqueduct and floor of the fourth ventricle were markedly deviated backward. The fourth ventricle was displaced toward the left. The left vertebral arteriogram demonstrated the basilar artery to be close to the clivus. The superior cerebellar artery was arched upward. In the later phases there was a stain immediately posterior to the basilar artery at the level of the posterior clinoid and clivus. In the frontal projection the posterior cerebral and superior cerebellar arteries were arched upward.

The patient was admitted for the second time in 1962 with progressive symptoms. Her gait and coordination were more impaired; blurring of vision was noted. Neurological examination showed, in addition to increase in the previous findings, decreased left corneal reflex, deviation of the tongue to the right, and weakness of the right extremities. Nystagmus was present on lateral and vertical gaze. Opticokinetic nystagmus was absent.

Lumbar puncture yielded a pressure of 250 mm of water. The protein was 192 mg%. The audiometric examination revealed a total unilateral hearing loss on the right. The electroencephalogram was normal.

Right suboccipital craniotomy was carried out. A firm meningioma was found in the right cerebellopontine angle. The capsule was incised and the contents removed. Tumor was removed from the internal auditory meatus. The capsule of the tumor was coagulated but capsule lying on the brain stem was not disturbed. The origin of the tumor from the junction of the medial side of the petrous pyramid with the tentorium cerebelli was coagulated. Postoperatively the patient improved steadily. Facial pain did not recur.

Discussion

Both of these patients harbored right cerebellopontine angle meningiomas which arose from the petrous pyramid. Revilla has noted a predominance of right cerebellopontine angle meningiomas as opposed to those arising from the left side (7). These tumors caused contralateral left facial pain which each patient had. It is noteworthy that this symptom occurred toward the middle

of the patient's preoperative course. In one case the pain was severe enough to necessitate the use of narcotics; in the other case it was less severe. It is likely that contralateral symptoms occur more frequently than is generally appreciated.

In the first case reported, the left facial pain started six years after the appearance of unsteadiness of gait. The pain resembled *tic douloureux* in that it was sharp and lancinating. It was aggravated by swallowing. Narcotics gave only partial relief. Objective evidence for involvement of the left cranial nerves was slight. There was more evidence for involvement of the right side of the brain stem; right facial weakness was present and the right caloric response was diminished. In the second case reported, the pain began two years after the appearance of headache. The patient complained of burning left facial pain and left orbital pain. At this time there were signs pointing to involvement of the right cranial nerves. By the time of the patient's second admission this pain had subsided spontaneously.

In the cases recorded in the literature, contralateral trigeminal neuralgia has varied from excruciatingly severe pain to only moderate severity. It has resembled true trigeminal neuralgia in character in that there has been no sensory loss. Precipitation of pain by movement and characteristic trigger zones have been described in the literature.

There has been great variability in the corneal reflexes. They have been present bilaterally, absent bilaterally, absent ipsilateral to the tumor, or absent contralateral to the tumor. Hypacusia, ipsilateral to the tumor, has been mentioned in two cases; this finding was also noted in our two cases. Caloric responses, ipsilateral to the tumor, have been diminished in our cases.

While contralateral trigeminal neuralgia is interesting from the clinical and pathological point of view, its significance is emphasized when surgical therapy is considered. In this situation it is of utmost importance to discern the true nature of the contralateral trigeminal pain, to ascertain the site of the tumor by study of all neurological signs present, to establish the anatomical relationships by neuroradiologic procedures, and to intervene surgically on the correct side.

In addition to contralateral trigeminal neuralgia, other contralateral signs such as trigeminal hypesthesia and/or deafness may be present. In reviewing monographs on posterior fossa meningiomas such contralateral signs are occasionally mentioned. Cushing and Eisenhardt (8), in their group of sub-tentorial and recess meningiomas, discuss three patients with contralateral manifestations (Table III, Cases 1, 4, 6). In these cases the tumor arose from the lateral or sigmoid sinus. D'Errico noted three cases in which hypesthesia of the face was present, out of ten cases of meningioma of the cerebellar fossa (9). Cazzato (10) described in detail a case of a meningioma of the lateral wall of the left posterior fossa which caused trigeminal and right acoustic deficit (trigeminal neuralgia was not present). Apparently the homolateral fifth and eighth cranial nerves were intact. Brown and Love, reviewing 55 cases of meningioma of the cerebellopontine angle, noted bilateral hearing

loss in 15 cases, bilateral corneal anesthesia in 12 cases (one case had only contralateral corneal anesthesia) and two cases of bilateral facial weakness (11). Other papers discussing meningiomas of the posterior fossa have included cases in which similar findings were present (12, 13). In addition, contralateral trigeminal hypesthesia has been recorded in cases of acoustic nerve tumor (14, 15).

As far as pathophysiology is concerned, it is apparent that displacement and rotation of the brain stem produce stretching or compression of the fifth nerve which leads to trigeminal pain. Castellano and Ruggiero point out that the trigeminal nerve is most easily injured since it is pushed against the sharp superior margin of the petrous bone (16). They have illustrated lateral displacement and rotation of the brain stem in a case of meningioma of the cerebellopontine angle (Fig. 52). Rotation, lateral, forward or backward displacement of the brain stem may take place. Displacements of this type have been illustrated in the literature. Russel and Bucy (13) include a photograph (Fig. 4) of a meningioma of the lateral recess with distortion of the pons. Bilateral signs, including trigeminal hypalgesia, were present. In a case of acoustic neurinoma Cushing (14) illustrated the displacement of the brain stem with stretching of the homolateral and kinking of the contralateral trigeminal nerve (Figs. 194 and 195). This patient also had bilateral hypesthesia.

Hamby's description of a cerebellopontine angle meningioma is of interest. The patient was a 54 year old woman who suffered, in addition to other symptoms, severe paroxysmal pain in the right ophthalmic division. Exploration of the right cerebellopontine angle showed the right fifth nerve to be running directly downward instead of upward and forward. Its lower end was tightly compressed between the pons and the incisura of the tentorium. The root was sectioned. Displacement of the pons caused it to appear enlarged, not unlike a pontine glioma. Autopsy revealed a meningioma $6 \times 4 \times 0.5$ cm in size in the left cerebellopontine angle which displaced the cerebellum and brain stem backward and to the right.

Doring reported studies of the histology of the entire brain stem in cerebellopontine angle tumors (17). He demonstrated that changes may occur on both sides of the brain stem in cases of unilateral tumor. He presented an illustration of bilateral gliosis in the descending trigeminal tracts which is germane to our present discussion of contralateral signs. In general, he found rather extensive chronic changes in the brain stem and attributed high mortality in operations to these alterations.

The vertebral angiogram plays a role in the diagnosis of cerebellopontine angle tumors. Upward displacement of the first part of the superior cerebellar artery has been described by Kihlani and Silverstein as useful in ascertaining the presence of an extra-axial tumor of the cerebellopontine angle (18). Olsson has described changes in the vertebral angiogram in acoustic nerve tumors (19). From an experimental point of view, Cooper and Stellar were unable to confirm displacement of the brain stem by vertebral arteriography in an

acute animal experiment (20). They inflated balloons in the cerebellopontine angle in dogs and produced reversible signs such as ataxia and loss of the ipsilateral corneal reflex. However, it is perhaps unlikely that such an acute experiment could duplicate the slowly progressive changes that occur with an enlarging tumor.

We wish to distinguish contralateral involvement of the fifth or eighth cranial nerves due to an angle tumor from bilateral cranial nerve signs due to a benign or malignant midline tumor. Meningiomas arising from the clivus or tentorium or pontine gliomas, as well as other midline tumors, may cause bilateral involvement of the cranial nerves. Another condition which must be distinguished is bilateral acoustic nerve tumor which obviously may produce bilateral signs. Alajouanine and associates have given an interesting example of the pneumoencephalographic picture in such a case with lifting of both cerebellopontine angle cisterns (21). Obrador has recently described the surgical therapy carried out in such a case (22).

Summary

Two cases of meningioma of the cerebellopontine angle producing contralateral trigeminal neuralgia are reported. Contralateral trigeminal neuralgia is a rare but important symptom; its severity may focus attention on the side opposite to the true site of the lesion. It should be evaluated in the perspective of other neurological signs and symptoms and neuroradiologic studies. Care must be taken so that operative intervention is directed to the side of the tumor. Only seven such cases, five meningiomas and two acoustic nerve tumors, have been reported previously in the English and European literature.

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The Responsibility of Being an Obstetrician and Gynecologist

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A psychiatrist addressing you on your responsibilities might easily be considered presumptuous so let me hasten to say that the title should be extended to read "as seen by a psychiatrist."

I do not aim to take a straight course but will meander in this or that direction, and at random touch upon what I think are important matters. We shall speak of the social responsibility, especially in the changing world in which we live, we shall touch upon the moral responsibility and in passing may wonder how medical schools select students both of the highest intellect *and* the highest character; we shall comment on the legal responsibility in regards to those instances requiring our attention in addition to the Medical Practice Act which regulates the relationship between physician and patient—and finally we shall touch upon some matter of practical importance.

Just to mention one aspect of our social scene: We are witnessing a significant change. Until recently the physician as an individual visited the family of which his patient was a member, and it was within the home, in the family setting where the physician and the patient met. This situation became reversed when the doctor stopped visiting the family and began to see the patient either in his office or in the hospital; while formerly the physician as an individual was confronted by the family as a group, now it is the patient as an individual who is confronted by the doctor, who now in turn is surrounded by *his family*, namely, all those persons who form the medical team.

In most instances, the family represents a source of strength; being taken out of the family setting reduces the strength of the patient and increases his need for emotional support. When the patient reaches the office or the hospital, he is not met, however, by the physician who by his education and makeup is prepared and ready to give the emotional support the patient needs. Instead, the patient is met by a member of the doctor's medical team, a person who is specially and highly trained in his subspecialty, but poorly or not at all trained in understanding the emotional needs of the patient and in responding empathically to those needs.

Although most every physician in the course of his life goes through the embarrassing, humiliating, and upsetting experience of being a patient—albeit a special patient being a member of the elite profession—once he is back on his feet again everything is quickly forgotten.

In preparing for the establishment of a new medical school, as we currently are at Mount Sinai Hospital, we are faced with an almost impossible

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task. Side by side with an evermore increasing replacement of the physician by machines, has grown the realization that emotional factors are not only important in the causation of illness and disease but that emotional factors also play an equally important role in the patient's improvement and road towards health. Therefore, the physician of the future needs to be a person highly skilled in all the mechanized aspects of medicine while at the same time he has to be fully aware that human needs can only be satisfied by other human beings.

Few of us can fully realize what the practice of medicine will be like when the skill of a computer machine will compete with or even exceed the skill of the average physician. How easy it will be to forget that the most important drug the physician has to prescribe—is himself. How many physicians will be like the bottle in Alice in Wonderland that had a label "drink me." How many of us will know the pharmacology of the drug called 'doctor,' its therapeutic doses, its side effects?

As you know, in psychiatric practice, especially in those instances where no drugs are used at all, the therapeutic relationship is based on the skillful use of himself by the physician. I believe there is no specialty in addition to psychiatry, where this understanding is *more* important than in obstetrics and gynecology. When used skillfully, this relationship becomes therapeutic; in reverse it can be harmful.

Why does an obstetrician-gynecologist have to understand the nature of the relationship between him and his patient any more than any other specialist? The reason lies in the nature of his patient's illness and in the nature of the organ system for which she seeks the physician's help.

All this can be summed up in one word: sex, of course in its widest sense. His is a specialty that deals with the physiology and pathology of the reproductive system. Although the sexual act represents only a small part of the reproductive cycle, there are numerous conscious and unconscious links that tie sex to every phase of the reproductive cycle.

Therefore, it is the privilege and the responsibility of the gynecologist to 1) understand sexual matters, 2) to inquire into them, and 3) counsel the patient regarding them. More about that later.

Let me start out by describing first the doctor-patient relationship. There are two aspects to the doctor-patient relationship—a realistic and an unrealistic one. The former is the actual situation in which one person who needs and wants help to relieve discomfort, pain, symptoms, or complaints seeks the help of another person, the physician, who is not only trained to give help but is also interested in doing so. Although the physician is representative of a category, not all physicians are alike. Like apples, some are hard and some are soft, some green and some ripe. A patient's complaint that a physician is "too hard" on her could at times be an accurate, objective appraisal. There are many factors which determine the way a patient relates to a physician: his title, reputation, skill, appearance, age, sex, and many others.

Regardless of whether or not we recognize it, there is another element to the physician-patient "rapport" which is less obvious and less realistic but ever-present and perhaps more important than the realistic relationship. This phenomenon, known as transference, plays a vital part in the therapeutic process. Transference means that the patient relates to her physician in a way in which she had related to an important person in her life previously, generally her mother and father. This is more or less independent of any of the physician's qualities. Transference may manifest itself in positive or negative feelings towards the physician or a combination of the two. At times one side of this double feeling (ambivalence), although present, is not openly expressed.

The patient may look upon the gynecologist not only as a healer but also as a giving mother. By the same token the patient will not only look forward to obtaining from her physician what she did not get as a child; she may also transfer to him the disappointments she experienced in childhood with either mother or father or both.

An important aspect of the transference in the obstetrician's patient is the fact that it is to a greater extent of a sexual nature than in other specialties. Sexual feelings and wishes, as well as fears, are regular occurrences as part of transference. Since your specialty deals with the physiology and pathology of the sexual organs you must be constantly aware of this aspect of the physician-patient relationship. Aside from the psychiatrist, there is no physician as much exposed to the affectionate feelings of his patients as the obstetrician-gynecologist. To be "made up to" by young attractive women is a boost to the vanity of most men. Having learned about the basic facts of transference, the obstetrician should take this in stride, realizing that part of this "spontaneous" affection might be a distant echo of the feelings the woman had as a child towards her father. But this is only half of the situation. Regardless of whether or not he is flattered, the obstetrician must be aware of the fact that part of this affection his patient displays toward him also represents her wish as a child to be close to mother. The need for such attachment towards mother—at times takes grotesque forms. Once an obstetrician called me, partly in embarrassment and partly in despair, because of a strong infatuation a patient had for him. A woman he had delivered could not let him out of her sight; from early morning, she wheeled her baby in the carriage around and around the office building where he practiced just to catch a glimpse of him arriving or leaving. He was embarrassed because he could not imagine what he had done to bring about such a reaction, and he was in despair because this woman's behavior was beginning to interfere with his practice.

Regardless of whether or not the patient sees in you her idealized father, her fantasied lover, her protective mother or her frustrating and disappointing mother, these feelings leave the patient wide open to be hurt. Because of this increased vulnerability, the demands on you are greater and so is your responsibility. Although there are differences of degree, and I emphasize this, nevertheless, a patient with such feelings towards you is similar to a patient

under anesthesia, under the influence of drugs or under hypnosis. Every physician, you in your specialty in particular, needs to work constantly on increasing his understanding of his relationship to his patient.

Because of the intimate nature of the sexual organs of your patient, and their use for sex as well as reproduction, you are more likely than not to be the first physician in whom a woman may confide. This is borne out by some of the patients who are referred to me by your colleagues for consultation. To whom is a young woman going to turn if after a few years of marriage her husband turns away from her, rarely if ever having sex with her and is being seen masturbating by his wife? When she finally found courage to tell the obstetrician about it he realizes that he is dealing here with a problem beyond his ability to cope. *Your ability to listen gives your patient the freedom to speak.*

There is no question that it is difficult to be sympathetic and understanding and yet to remain objective. Perhaps the closest intimacy in the doctor-patient relationship—at least on a physical level—is to examine the patient vaginally. In the course of his training in medical school and later as intern and resident, the physician has learned to establish a variety of defenses which are necessary in dealing with the sick. When examining a patient, the sensitive touch of his fingers, used in love-making to give and bring pleasure while fondling the genitals of a woman, this same sensitive touch has now become a tool with the aim to diagnose and to heal. The degree and perfection which may be achieved in changing the desirable "body" of a woman into an object of medical interest at times depend on the age—of the patient and of the physician.

The distance and detachment of the physician from his patient's physical symptoms, his neutrality in regard to them, is essential for the practice of medicine. The maintenance of such an attitude becomes quickly weakened, when the patient's illness creates a resonance in the physician because he or a member of his family is suffering from the same illness. For instance, a physician who just lost his wife due to cancer of the ovaries would be superhuman—or rather less than human, if he would remain objective when finding the same condition in his patient. The personal experience in the life of the physician alters the responsivity in him. It will take time till the resonance becomes lessened and the doctor becomes again properly insulated and his objective judgment reestablished.

However, regarding matters of sex, in the widest sense, this difficulty of remaining neutral holds true even if we are dealing with conditions not necessarily labeled pathologic. When it comes to emotion and sex, the possibility of setting up reverberating responses in the gynecologist are present to some degree all the time, in most everybody.

It has been my observation that it is easier to establish defenses in order to remain objective regarding the physical examination of the patient, than to reach the same degree of objective interest when it comes to discuss sexual matters with patients. Similarly to a woman who is said to be able to give of

her body but not of her soul, so is it more difficult for the woman patient to talk about her sexual wishes, fears, feelings, and reactions than to be examined—I almost said sexually. A woman can remain completely passive when examined; she can detach herself from the situation, close her eyes to it in every respect. When examined physically it is the doctor's job to tell her; in discussing sexual matters the reverse is true: she has to take an active part, she has to tell the doctor. But no woman will tell you if you are not ready, not willing or not prepared to listen.

In order to be a good physician it is not necessary to practice medicine for altruistic reasons only. It is quite compatible with the responsibility of a physician that his chief motivation is to give service to his patient and that service comes first and profit second. When I said earlier that there should be a continuous self analysis, it is with the aim in mind to discover those hidden, at times rather subtle, motivations which interfere with the primary aim of helping the patient. The motive that has been most widely publicized and that has hurt the image of the physician most, is at the same time the easiest to recognize; namely, practicing for financial gains.

Yet there are other motivations—quite acceptable, at least within the medical fraternity, that might interfere much more with the primary aim of helping the patient; for instance putting scientific interest first. I'm sure that you are as well acquainted with this particular problem as you are with an equally important one, namely, when there is a conflict regarding a patient in the hospital between education of the physician versus service to the patient. I am neither holy nor wise, and therefore I do not have answers to all those questions, but I do think that every physician has to face them honestly. Should a hysterectomy be performed because the residents require it for their training if the indications for it are not clearly given? To what extent does the physician feel, unconsciously of course, that the patient is his property, rather than that he is in the service of the patient?

The moral and legal issues raised in regard to experimentation done on patients is probably too well in your memory. Whenever such experimentation is done with disregard for the patient, man has lost his value and his dignity. The physician for whom the patient has lost human value, has lost as much within himself. Irresponsibility does not only extend to financial and scientific motivations interfering with service to the patient, there are others, personal ones, known only to yourself. Of a number of them I shall mention only narcissism, prestige, and sexual gain.

A physician should not use his peculiar relationship to his patient to get either financial gains for himself or the institution in which he works, nor should he use this dependent relationship to get the patient's permission to experiment with him. The same holds true for every kind of sexual relation. Consent by the patient given under conditions of the therapeutic relationship is not *free* consent.

In the give and take of the therapeutic relationship it takes some time until it becomes established what the patient wishes to get from the doctor

and what the latter has to offer to the patient. I like to give an example from my own practice to illustrate this tug-of-war between doctor and patient.

I had a young schizophrenic girl in treatment, a very gifted person whose days are spent in submitting to day-dreams. Although romantic on the surface, the sexual nature of these day-dreams was quite obvious. I wanted her to reveal the nature of her day-dreams, she refused, eventually she won, and I came to the realization that this young woman had to live her life completely asexual. To delve into the underworld of her fantasy would have brought her face to face with the impossibility of having a sex life. The next step was equally important. I had the patient and her mother in my office and I made it clear to the mother that in the foreseeable future her daughter will not be able to date, to go out with men and to plan for marriage. Both broke down crying, for different reasons. The mother because she was deeply disappointed, the daughter because she was finally liberated. My intervention protected the patient against the pressures from her family.

I believe a young obstetrician-gynecologist is well advised to keep in mind that some of his patients not only come because they need his help to have a baby but also to get his protection against family pressure to have a baby. Infertility is one of the symptoms to be understood from this point of view. The woman who chooses to remain single is the easier one to handle than the married woman who beginning with dyspareunia and ending in miscarriage goes through the gamut of reproductive failures. At times the specialist in your discipline fails to obtain an answer because he did not ask the right question. The responsibility to his patient at such times goes counter to the main stream of the culture in which he and his patient live. That patient is the exception who will tell you that she is in a conflict between not wishing a child and the pressures from her husband or family to have one.

The physician in your specialty is confronted with a particular responsibility when a patient has a need to be mutilated and uses the physician as the instrument to mutilate her by operating on her. In those instances where the patient had everything that is removable cut out, such a case of polysurgery is not difficult to recognize. In other instances it is most difficult. Let us take the instance of a patient with recurrent bleeding for which the patient requests a hysterectomy and the physician reluctantly agrees although the indications for such an operation are not quite given. Should the healer become executioner?

In such a situation the Hippocratic and the legal responsibility coincide. It is for the physician to see to it that the patient gets the maximum benefit—and, we may add, even in those instances where the patient is "dead set" on her own destruction.

Although I expect little argument to the contention that it is the patient and the patient only whose total welfare, physically as well as mentally, is the concern of the physician, there is an exception to that too. I am referring to those instances where the obstetrician is not dealing with one individual but

with more than one: a woman who is pregnant or a woman who has delivered the baby.

I shall only mention, without discussing in detail, those situations where the life of the mother and of the fetus are at stake, and the obstetrician has to make a life and death decision; whose life to sacrifice—whose life to save.

I shall rather speak about matters of equal importance to psychiatrist and gynecologist. It relates to the prevention of pregnancy, to therapeutic abortion and to a situation related to it, *i.e.* the decision about the child born out of wedlock.

As to the indication for a therapeutic termination of pregnancy, I believe that it is important for you to understand some of the problems that are involved when such indication is made on psychiatric grounds. There is hardly a situation which more severely tests the professional, legal, moral, and social responsibilities of a physician than a therapeutic interruption of pregnancy.

There are good reasons why it is more difficult for a psychiatrist than for any other medical specialist to validate an indication for interruption of pregnancy. Those dealing with the functions of bodily organs need only to assess the physiologic burden that pregnancy places on a particular organ system of the body. The cardiologist, for instance, knows that the added burden pregnancy puts on the heart, comes to an end with childbirth. The situation is different in the field of psychiatry. The psychiatrist knows that whatever the pregnancy means regarding the mental health of the woman, childbirth will not be the end of the problem but the beginning of another problem, namely the complicated relationship once the baby is born. This consideration makes it clear that the psychiatrist must set his sights at a more distant point in the patient's life course. A woman who is serious about her threat to kill herself unless the pregnancy is interrupted, is expressing such intense reaction not only because of a fear of the pregnancy itself or of the childbirth, but often is thinking about the child that is going to issue from this pregnancy. If we could be certain that a woman would kill herself *after* the child is born, are we not justified in considering pregnancy as such a threat to her life as if she would threaten to kill herself *before* the child is born? In addition, the very hostility and aggression which some women turn towards themselves while they are pregnant, may after childbirth be turned with the same strength toward the child. This places in proper perspective the frequently expressed thought, "Why not put the patient in a mental hospital where one can be certain that no harm will come to her?" It becomes obvious that this would be the beginning of an endless problem, rather than a solution.

Regarding the other problem: that of a child born out of wedlock from a chronically psychotic woman. Although the responsibility for a decision lies with the psychiatrist, I believe it would be of value for the obstetrician to be knowledgeable about this problem. Without such knowledge he might become unwittingly an instrument in the hands of a manipulating patient. If such a woman has a child, the physician is confronted with an unusual situation. He

not only is responsible for the welfare of his patient, the woman, but also for her child. The physician becomes the delegate of society, of the community; his loyalty is now being divided between considering the benefits for his patient and the benefits for the child. He has to understand clearly that the woman who is psychotic and is going to raise her child all by herself is most surely going to harm the child. The decision in such a case is based on the consideration that leaving the child with its mother is going to hurt the child more than it will help the mother, and in taking the child from the mother will hurt the mother little and help the child much.

Let me close by thanking you again for inviting me to speak to you and by wishing you happiness and success in your professional life.

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Institutional Care Facilities for Older People in New York City

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Recent developments with respect to increased availability of funds for the care of aged persons are creating a demand for required medical services, including long-term care. This paper is an attempt to summarize some useful information about the major institutional facilities for long-term care in the metropolitan area, and may be of use to physicians who have family practices or who in their specialties must deal with dispositional problems. New and expanded services reach aged persons through Medicare—the Federal program of health insurance for persons 65 and over, and Medicaid. Medicaid is the Federal-State-local program for persons *of all ages* who are unable to meet their medical bills and at the same time pay for their other needs. This is judged in terms of a maximum annual net income contingent on family size, number of wage earners, and related criteria.

For optimal use of the funds provided by these programs in the patient's interest, it is important for physicians in general practice and specialists in medicine to have a clear understanding of the role and functions of the two types of existing facilities, in addition to state mental hospitals, currently housing most of the institutionalized aged in metropolitan New York City—nonprofit voluntary homes for the aged and nursing homes and proprietary nursing homes—as well as some of the characteristics of these institutions and their populations. Such information may be helpful in the matching of patients and site of care on the basis of patient need.

I. Public Medical Care Programs for the Aged

Medicare covers 1) basic hospital insurance with specified benefits for hospital care, extended care after hospitalization (including both home health care and post-hospital care in an extended care facility), and out-patient diagnostic care; 2) voluntary supplementary medical insurance with specified benefits for other medical care, namely, doctors' services, other

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This paper is based on data and experience from a current 10-year longitudinal survey (by the Office of the Consultant on Special Services for the Aged) of proprietary nursing homes, homes for the aged, and state mental hospital populations in New York City. (Data from the survey are appended for reference.) Since these institutions are in a period of transition, changes and new developments may well have occurred since the preparation of this paper. There have been recent legislative cutbacks in Medicaid affecting eligibility, particularly of adults between 21 and 65.

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medical services and supplies and home health services. This insurance program has deductibles and time limits; in addition, many services are excluded. Private health insurance plans can be utilized to fill in the gaps in the Medicare program, and to provide varying supplementary benefits, by older people who can afford to carry such insurance.

For eligible older people of limited means, Medicaid, which replaces the Medical Assistance for Aged Program (MAA), provides relatively comprehensive medical care—including psychiatric care—without the exclusions, time limits, or the kinds of deductibles built into the Medicare program. Moreover, not only is the coverage under Medicaid much broader than was the case under the former MAA program, but the income ceilings for eligibility have been greatly liberalized.

Especially noteworthy in connection with Medicaid is the Federal provision which specifically eliminates the legal requirement that children are responsible for the medical bills of their parents; thus, only the income of a spouse can be considered in determining eligibility. Of added significance is the extension of this provision by recent New York State law to exempt children from responsibility for all kinds of support for their parents. Consequently, in this state, children are no longer legally responsible for contributing in whole or in part to the cost of maintaining their parents either in their own homes or in institutions.

These changes in Federal and State laws affecting contributions from children have brought about a marked increase in the number of institutionalized aged and aged persons in the community eligible for public assistance for maintenance, as well as for medical assistance under Medicaid. All public assistant recipients and former recipients of MAA have been declared automatically eligible for Medicaid by the City Department of Welfare.

Because of the high and rapidly mounting cost of institutional care, the aforementioned changes are especially important for children who formerly carried total or partial responsibility for the support of institutionalized parents. Moreover, the prohibitive cost of care may have prevented some institutional placements of parents by their children heretofore, even when such care was urgently needed.

II. Description of Homes for the Aged and Nursing Homes

HOMES FOR THE AGED are nonprofit voluntary institutions providing protective residential care to older people who enter them with a view to remaining residents for the rest of their lives. These homes are operated under the supervision of the New York State Department of Social Services and the New York State Department of Health which have set forth principles, rules, and recommendations applicable to residential care in such facilities.

The homes vary greatly in the extent of medical and nursing care they provide: some have complete programs including both approved infirmary

and approved hospital care; some give only minimal residential care. Thus, some homes are also hospitals in almost every sense and comply with licensing and other requirements for such institutions; others are merely congregate residences with varying personal care services. The number of homes providing social services is increasing, but such services are still lacking in many homes. The State Department of Health supervises the approved infirmary units of homes for the aged and the Department of Social Services supervises their non-medical areas.

The homes also vary greatly in bed capacity—from a low of about 20 beds to a high of over 1,000 beds. There have been no lasting changes in the total bed capacity of these homes during the past decade or so. In fact, the number of beds decreased somewhat in the 12-year period between 1953 and 1965, from some 9800 beds to about 9400. Varying estimates of so-called infirmary or "nursing home" type of beds in these homes in 1965 ranged from about 3500 to close to 5,000. Generally classified with homes for the aged are three nonprofit voluntary nursing homes in the Metropolitan area.

Homes for the aged are usually run under sectarian auspices by private philanthropic boards composed of lay people. These boards often have admission committees who review applicants and make decisions about admissions. Consequently, admission policies and practices, including financial arrangements, differ markedly from one home to another according to the Board's ideas of whom they wish to serve or who will "fit in," as well as with what problems the staff is equipped to deal, bed capacity, and type of care available. Thus some homes may exclude persons simply because they are objectionable to the board or the management, or because they are dependent on public assistance. Moreover, since the inception of Medicare, some homes have tended to exclude beneficiaries of this insurance program and, more recently, participants in Medicaid as well, preferring to admit persons who can defray all of their expenses independently without participation in either of these public programs.

In the main, homes for the aged have sectarian admission policies, but there are some exceptions; nonetheless even in nonsectarian homes, persons tend to select homes or to be selected according to their religious affiliation. Also, unlike nursing homes and state hospitals, white persons have customarily comprised virtually the entire population of homes of this type. While the all-white pattern probably still holds for the most part, there are recent indications of a beginning trend toward the admission of some nonwhite persons—and persons of different religions—to some homes, particularly to newly opened facilities.

Closely associated with differences in the sectarian auspices of homes for the aged are differences in the social and economic characteristics of the residents. Thus, while the populations of the Jewish-sponsored homes tend to be fairly homogenous, and this is true of the population of the Protestant-sponsored homes as well, there are striking differences between the char-

acteristics of the two groups as a whole. The Jewish-sponsored homes tend to admit proportionately more "younger" people, many more men, many more widowed and also more still married persons, many more foreign born who subsequently became naturalized citizens, many more persons with no or little formal schooling, more former non-earners, and more financially dependent persons. Conversely, the homes under Protestant sponsorship tend to admit more chronologically older people, many more women and very few men, many more single and few still married people, many more native-born citizens with relatively high educational backgrounds, and more financially independent persons, including more former earners. In addition, residents of the homes under Jewish auspices more often have a number of living children when admitted; they often assume full or partial financial responsibility for the cost of institutional care of their aged parents. Conversely, on the other hand, residents of the homes under Protestant auspices are mainly childless or have only one living child and are more likely to be self-supporting when admitted. (Comparable facts are not available for the residents of the Roman Catholic homes.)

Financial arrangements at the time of admission according to each home's policies, range from free care (members, or persons unable to pay), partial payment according to ability to pay, or full payment of board and any extra charges at the going rate in a given home. Such arrangements may also include entrance fees of varying amounts, transfer of personal property and other assets, including current income, as well as contracts for life care.

While public assistance recipients are not accepted in all homes, there are now more of these recipients in the homes that formerly admitted them. Moreover, some homes that in the past excluded public assistance recipients now admit them. This change in policy not only affects new admissions but the eligibility for public assistance of long-time residents as well. In addition, a significant increase in the number of public assistance recipients took place when the former Medical Assistance for the Aged Program (MAA) went into effect in 1961; under this program some residents receiving approved infirmary care became eligible for public aid. Also contributing to this increase in welfare recipients in homes is a fairly recent liberalization in eligibility requirements for public assistance, which enables residents who made life contracts with homes when admitted—formerly ineligible for public assistance—to receive such aid, based on review of individual agreements by the New York City Department of Social Services, if the personal financial resources turned over to the home have been exhausted. Both of these measures have tended to strengthen the financial structure of the homes involved.

Effective early in 1967, as previously indicated, all recipients of public assistance and of the former MAA program became eligible for assistance for medical care under Medicaid. Also, residents of homes for the aged formerly dependent on their children in whole or in part for meeting their medical bills as well as for the cost of their maintenance are now eligible for

public assistance from the Department of Social Services and Medicaid. In view of the fact that in the past many residents of homes for the aged, especially in the Jewish-sponsored homes, depended on their children for support, either wholly or to supplement inadequate incomes from independent sources, this change probably applies to a sizable proportion of the population of homes of this type. Therefore, in all likelihood, only a relatively small proportion of the current residents of homes for the aged—persons of independent means not qualified for Medicaid—may have to rely on private health insurance or make direct outlays from their own financial resources to pay for essential medical services not covered by Medicare, if medical care is not provided in the homes in which they reside, or to supplement the care available.

Another factor of considerable importance, in relation to improvement in the financial structure and services of the homes caring for public assistance recipients, has been a series of increases in the monthly rates paid for their care in an effort to keep pace with mounting costs. Such rates vary from home to home, according to the type of care provided (domiciliary or approved infirmary) and the specific services available in a given home, within established monthly *ceilings*. Upward changes in rates since September 1960 brought monthly ceilings in 1967 to \$340 from \$200 for domiciliary care and to \$510 from \$300 for approved infirmary care.

As a rule, applicants are interviewed to determine their eligibility and interest in living in a particular home, and pertinent social data are likely to be recorded in most cases. Often there is a considerable lapse of time—from 3 months to as long as 3 years—between application and the admission of eligible persons. This is especially true when interest is centered on admission to a specific home with a waiting list. In general, relatively well people have the shortest waiting period while the sickest must wait the longest, particularly if they need nursing care. For this reason alone, some eligible applicants on waiting lists, of necessity, go to nursing homes instead. Residents of homes for the aged are most frequently admitted from their own or a relative's home.

PROPRIETARY NURSING HOMES are privately owned commercial institutions providing protective residential care, personal care, nursing care, and other services (excluding medical care) for persons requiring supervision of their health conditions who cannot remain at home, and who in the judgment of their physicians do not require active treatment in a hospital. The homes are licensed by the New York City Department of Hospitals and operate under the jurisdiction of this department according to a code of standards approved by the New York City Board of Hospitals. In recent years there have been a number of much needed improvements in the administrative, physical, and service aspects of nursing home care; the outlook points to a continued change for the better. These improvements stem mainly from the adoption of a new and greatly strengthened code adopted in February, 1963. However, many changes contributing directly or indirectly

to improved patient care and safety were introduced in 1962, prior to the formal adoption of the new code.

The bed capacity of nursing homes ranges from 15 beds to over 300. The present code states that "patients' rooms shall contain no more than four beds." In the five year period from 1953 to 1958 the bed capacity of these homes more than doubled, increasing from about 4000 to over 9000 beds. It remained constant in 1959 and 1960, then dropped somewhat in the five-year period from 1960 to 1965. However, new homes now under construction or being planned are expected to bring about a gradual and probably substantial increase in the bed capacity of this type of facility. (Also expected to more than double in the next five years are the number of beds in *public infirmary areas* of hospitals and other public facilities, increasing the bed capacity from about 2000 beds to 4250-4350. Existing beds are now occupied mainly by older public assistance recipients.)

Most patients in nursing homes are older people with chronic illnesses and disabilities; many—about 75% in 1965 and probably more today—are recipients of public assistance, receiving full or supplementary financial assistance as well as medical care through the New York City Department of Social Services. In fact, in the past decade or more the role of the nursing home has shifted increasingly from a facility mainly serving private patients of various ages for relatively short-term care, to one primarily used for the long-term care of aged welfare clients. Thus, most nursing homes in the city are now largely "homes for the aged," operating in effect as sub-contractors and financially sustained chiefly by public funds. Moreover, despite a decrease in the total bed capacity of these homes the number of public assistance recipients has continued to increase.

There are indications of a possible reversal in this trend with attention now being given to the use of nursing homes for short-term convalescent care insofar as possible, and other facilities for long-term care. Also, when appropriate, foster-home care placements of public assistance recipients are being encouraged as an alternative to nursing home placements directly from general hospitals. This shift in emphasis may reflect recent thinking about the role of the nursing home as set forth in the new code which states that "Whenever possible patients shall be helped to return to their homes or other residential living arrangements." It may also be associated with the recent utilization of qualified nursing homes—the majority of these homes—as extended care facilities under Medicare. However, up to the present time there continues to be an insufficient number of facilities and vacancies in the community to meet the needs of older people for long-term care.

Between 1961 and 1966 the medical care needs of public assistance recipients in nursing homes were met under the former Medical Assistance for Aged Program (MAA). Residents of homes who formerly participated in this program are now automatically qualified for more complete medical care under Medicaid. Of the small proportion of former private patients in

nursing homes—perhaps about 10 percent of their total population—also qualified for Medicaid, are those aged persons who were previously entirely supported by their children or partially dependent on children to supplement small amounts of independent income. Thus, currently the proportion of private patients in the total nursing home population with independent responsibility for meeting their own medical care needs under Medicare, supplemented by private health insurance benefits or direct outlays, is probably very low indeed.

Until 1962, medical care for public assistance recipients in nursing homes was provided by panel physicians on a case-by-case basis. Since that time there has been a basic change, gradually introduced, in the method of providing medical care to this large group of nursing home patients. The change is designed to provide comprehensive medical services to public assistance recipients on a continuing basis through the utilization of other city resources under contract. Three new approaches have been developed to accomplish this aim: 1) services from established group medical practice (HIP) in most homes; 2) hospital-based services in some homes; 3) so-called "community-based" services by teams of private physicians in a small number of homes. Agreements with local hospitals provide for the transfer of medical information with the transfer of patients from one level of care to another. In keeping with code requirements and policy, transfers to hospitals or other appropriate facilities are indicated for diagnostic study or for care or treatment of acute or severe illnesses or conditions which cannot be met in a home. Such intermittent returns to hospitals are fairly common.

In October 1960, uniform public assistance rates to nursing homes were set at \$230 monthly irrespective of differences in care, in the specific services provided, in the physical features and facilities, or in the special programs available. Since that time there have been a number of upward changes in rates to meet the cost of improved services and other increased costs. Moreover, these rates—now established by the State Department of Health—are no longer uniform. Instead, they are set home-by-home based on operating costs on which reports are submitted annually. For the July 1, 1967 to June 30, 1968 period, the effective rates for New York City homes range from \$390 to \$608 monthly. In 1967 the rates in the homes utilized by the City Department of Social Services ranged from \$399 to \$561 monthly. Rates for nursing home care paid by private patients are higher than public assistance rates; these rates vary from one home to another and often there are extra charges for special services as well.

Admission to a nursing home is more often from a general hospital than from the patient's or a relative's home. Generally, arrangements for admission are made by a relative, physician or interested agency. A public assistance recipient is placed in a home only with written approval. Interviews by nursing home personnel prior to admission are rare, and the social data obtained are meager; according to the new code each patient's non-medical

record must include, among other things, at least the following: name, age, sex, marital status, religion; also the place from which received, nearest of kin (or sponsor) and relationship, and the referring person or agency or other interested party. The new code also requires that, after a date fixed by the New York City Commissioner of Hospitals, each home employ at least one qualified social worker, full or part-time, or enter into an agreement with another recognized social or health agency or social service department of a hospital to provide patients with direct access to casework services. The role of the social worker in the nursing home setting is now under study.

Nursing homes admit fewer older people in the youngest age group (65-74) and more in the oldest age group (85+) than either homes for the aged or state hospitals; most persons are 75 and over when admitted. As is the case in the two other types of institutions, the great majority of admissions are widows and widowers, mainly the former, but nursing homes admit somewhat more never-married persons than either homes for the aged or State hospitals.

Through placements, chiefly by the Department of Social Services and to a lesser extent through self-selection, the older populations of individual nursing homes tend to be fairly homogeneous groups with respect to borough of previous residence and such factors as religious and cultural affiliations. However, these groups are more heterogeneous than is true of homes for the aged: persons of the three major religious faiths are found in many nursing homes and this also applies to non-white persons. In fact, the proportion of non-whites in the total nursing home population exceeds that of non-whites in the general aged population, 8 percent and 6 percent, respectively.

Appendix

SELECTED FINDINGS FROM CONSULTANT'S OFFICE SURVEY OF MAJOR NEW YORK CITY INSTITUTIONS FOR THE CARE OF THE AGED

I. *The Medical and Psychiatric Problems of Older People in Homes for the Aged, State Mental Hospitals and Proprietary Nursing Homes are Distinctly Overlapping.*

Contrary to the commonly prevailing impression that each of the three types of institutional facilities serves a separate and distinct segment of the older population with widely disparate medical and psychiatric characteristics, quite the opposite appears to be the case. Thus, regardless of type of setting, comprehensive initial examinations revealed that most institutionalized older people have psychiatric disorders, mainly some degree of chronic brain syndrome (Table I). However, the proportion with severe chronic brain syndrome (CBS) and CBS with associated disorders is greater in state hospitals than in the two types of homes (Table II). In addition to their mental impairments, it was found that most of the institutionalized aged also have physical impairments; the proportion with severe physical impair-

TABLE I

Prevalence of all Mental Disorders and of CBS, Total Group at Initial Examinations

All mental disorders	90%
CBS, All degrees	85
Mild	27
Moderate	31
Severe	27

TABLE II

CBS Severity by Type of Institution, Total Group at Initial Examinations

	Mild	Moderate	Severe
Homes for the aged	37%	28%	15%
Nursing homes	24	35	29
State hospitals	9	32	53

ments is highest in nursing homes. Further, a close relationship was found between the mental and physical functioning of older institutionalized persons, particularly among those in homes for the aged and nursing homes. Still another finding indicated that mental and physical functioning are greatly influenced—favorably or adversely—by the climate created in a given institution.

It is clearly evident from these findings that homes for the aged and nursing homes, as well as State hospitals, are important centers for the care and treatment of mentally disturbed older people.

II. The Mental and Physical Impairments of Older People Account only in Part for Their Admission to Institutions; Lacks in Social, Psychiatric, Other Medical and Related Services—Particularly of Home Care Services—Often Lead to Institutionalization.

The chief reasons given for admission to institutions were: 1) older people with disabilities were unable to care for themselves and there were no relatives, friends or others who could make living outside of institutions possible; 2) there were physical, psychological, social or financial problems with which older people were unable to cope in their present living arrangements without help not currently available.

Such reasons were given for more than half (57%) of the persons admitted to homes for the aged and also for a sizable proportion (40%) of those admitted to State hospitals. Significantly, such reasons were given for only a small proportion (17%) of the persons admitted to nursing homes in addition to clear-cut problems of physical disability.

Thus, closely related to institutional placement are such factors as lack of or breakdown in the socially supportive or medical services in the community that would have enabled some aged persons with impairments

TABLE III
Place of Residence from which Admitted by Type of Institution

	Own Home	Relative's Home	Nursing Home	General Hospital	Other
Homes for the aged	61%	26%	8%	3%	4%
Nursing homes	25	8	8	56	3
State hospitals	41	31	7	15	4

to remain in their own or in a relative's home, in a foster family home, or in another living arrangement in the community.

III. *Most Older People are Admitted to Institutions from Their Own or a Relative's Home, but unlike Admissions to Homes for the Aged and State Hospitals, more than Half of the Admissions to Nursing Homes are from General Hospitals.*

These findings again reinforce the fact that aged persons admitted to institutions generally require social and health care which today only under extraordinary circumstances can be provided in their own homes (Table III). The high proportion of admissions to nursing homes directly from general hospitals also points up the lack of short-term posthospital care facilities to provide suitable temporary care for older people following hospitalization. Thus, placements for long-term care in nursing homes may have been made in the past, when only short-term care was indicated, due to the lack of community facilities geared to provide temporary skilled nursing care.

IV. *Compared to the General Aged Population, the Elderly People Admitted to Institutions are Older and Poorer, with Many More Financially Dependent Persons.*

Both socially and economically the institutionalized aged comprise a highly disadvantaged segment of the city's total aged population. Factors contributing to the lower socio-economic status of the institutionalized aged are the high proportion of persons 75 and over, of women—mainly widows, of foreign-born persons—many with no or meager formal schooling, of non-earners, including former housewives never in the labor force, and former workers who held unskilled or only semiskilled jobs.

These findings strongly suggest that low socio-economic status contributes significantly to institutional placement. Advanced age and widowhood together with financial dependency appear to be important contributory factors (Table IV-VII).

Particularly noteworthy is the extent of financial dependency in whole or in part among admissions to nursing homes—about 90 percent, of which about 70 percent were totally or partially dependent on public assistance; the proportion of public assistance recipients among residents of nursing homes is even higher.

TABLE IV

Age of the General Population and the Institutional Population, 65 and Over, in Metropolitan New York

	General Population*	Institutional Population†
65-74	80%	40%
75-84	16	47
85+	13	13

* From 1960 census

† Prior to or when admitted to institutions

TABLE V

Marital Status of the General Population and the Institutional Population, 65 and over in Metropolitan New York

	General Population*	Institutional Population†
Married	49%	13%
Widowed	37	65
Div/Sep.	3	4
Never married	11	18

* From 1960 census

† Prior to or when admitted to institutions

TABLE VI

*Sources of Income of the General Population and the Institutional Population, 65 and Over in Metropolitan New York**

	General Population†	Institutional Population‡
Earnings	29%	1%
Social Security	49	33
Other public or private pensions	13	} 25
Interest & rent	16	
Other (excluding public assistance)	9	} 44
Public assistance	5	
Contributions from children and relatives	(included in other)	28

* Percentages overlap due to more than one source

† From "Characteristics of the Population and Labor Force in New York State, 1956 and 1957," New York State Department of Labor

‡ Prior to or when admitted to institutions

V. *Nursing Homes, as well as the Other Two Major Types of Institutions Caring for Older People, are Primarily Long-Term Care Facilities.*

Not only are homes for the aged and state hospitals long-term care facilities for the aged, but for a number of years this has also been true of nursing homes. In fact, nursing homes are now utilized by the City Department of Social Services on an extensive scale to provide indefinite or

TABLE VII

Financial Independence or Dependency when Admitted by Type of Institution

	Total Self-Support*	Self-Support & Dependency	Total Dependency†
Homes for the aged	49%	20%	39%
Nursing homes	9	18	72
State hospitals	60	3	36

* Social Security benefits or income from savings, pensions or investments, or both combined, except in the State hospital group which included some earnings only

† Public assistance or contributions from children or other relatives, or both; financial aid from private agencies insignificant

permanent living arrangements for aged public assistance recipients. In 1959, there were 5380 public assistance recipients residing in nursing homes; by August 1965, the number had increased to over 6000 living in 73 of 86 licensed homes (total bed capacity 8785).

Many nursing homes have qualified as extended care facilities under Medicare (effective in January 1967). In view of those developments, it is likely that some nursing homes may relinquish their role as facilities for the long-term care of the aged and instead become short-term care facilities only, under the Medicare program. In a highly illuminating discussion of this subject and its many ramifications, as well as of the whole field of institutional care for older people in the light of the Social Security Amendments of 1965 and other recent developments, G. Binder, Director of Adult Institutions, State of New York Department of Social Welfare (now Department of Social Services), concludes that "the extended care facility will take over the functions of neither the nursing home of the past nor the home for the aged but will be, in fact, a new kind of facility geared to provide relatively short-term hospital-type care." She states further "that nursing homes qualifying as extended care facilities may be removed from the field of truly long-term care." She also predicts that pressure for beds for extended care under Medicare will not get out of hand as is anticipated by many authorities; rather that there is likely to be a heavy demand for good quality domiciliary homes and institutions "where such medical and nursing needs as residents may have are met through planned use of general community resources" (1).

Significant in this connection is the recent emergence of another type of community facility for the care of the aged—namely, the institutional type proprietary adult home. These homes are congregate facilities accommodating five or more adults unrelated to the proprietor. They serve older, infirm or disabled adults who actually do not need nursing care but who do require a protective living arrangement and a range of personal care services beyond those usually offered to boarders and lodgers, such as help with bathing, dressing, feeding, and moving about.

As a result of recent legislation, the State Department of Social Services

has been given responsibility for inspection, approval, and supervision of these facilities. To utilize them constructively for the benefit of Public Assistance recipients, the City Department of Social Services has recently established a Division of Institutional Proprietary Homes for Adults within its Bureau of Special Services. This division is responsible for developing and operating a program which offers these facilities to clients in need of the care and services provided by these homes (and who prefer a larger and less intimate living arrangement to the family-type foster home for adults) and makes suitable placements through a central placement service following medical evaluation.

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Evolution and Pathogenesis of Discogenic Spine Pain and Associated Radiculitis as Seen in the New York City Fire Department

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As in many industries in which heavy labor is involved, the Fire Department of the City of New York has a significant problem in the disability caused by injuries, and to less extent, other conditions of the spine and adjacent musculofascial structures of the back. This is indicated in the loss of many man hours from work, requiring increase in the numbers of workers, or working short-handed. An added source of economic loss is the frequency of permanent disability with premature limited service assignment or retirement, and large compensation and premature pension costs. The frequent line of duty connection with such injuries, with associated greater pension and sick leave costs, adds to the problem. Since the men enter the Department in young adult life and do not retire until a minimum of 20 years, and often 25 or 30 years, has elapsed, the entire situation is complicated by wear and tear changes of everyday living, repeated minor or major traumata, and the degenerative effects of aging. In the year from September 1, 1957, to September 1, 1958, there were 1,687 service connected injuries in the Department. These were divided as shown in Table I.

The back conditions constituted 12.5 percent of all the injuries of the year, and 19.5 percent of the significant injuries. The working force at the time was about 11,000 men. Since many of these back injuries involved prolonged periods of disability (with sick leave at full pay), the economic loss is obvious. Consistently, cervical spine and associated neck injuries have been about one-fifth of the total back injuries. Over two-thirds of the rest have been related to the low lumbosacral region. It is, therefore, timely and important to consider the possible factors affecting the prevention, diagnosis, and management of these conditions to minimize the human and economic loss. In one typical year from March, 1963, to March, 1964, 51 men were assigned to limited service permanently, to be prematurely retired because of back injuries and related conditions. This means that during that year they were finally judged to be permanently partially disabled so that they would never be able to return to full fire-fighting duty. Many continued to serve at light duty assignments not involving strain or exertion until finally retired on three-quarters of their final compensation, if attributed to line of duty injury, as compared with half pay for non-line

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TABLE I
Incidence of Service Connected Injuries

Lacerations and contusions	537
Sprains and strains	150
Burns	124
Eye injuries and inflammations	123
Heat exhaustion and over-exertion	87
Fractures and dislocations	53
Herniae	22
Miscellaneous superficial and uncommon injuries	383
Spine or back injuries of all sorts: 210	
Cervical	40
Thoraco-Lumbo-Sacral	170
Total:	1,687

Back conditions constituted 12.5% of all the injuries of the year, and 19.5% of the significant injuries.

TABLE II
Classification of Back Conditions of Men Judged Permanently Disabled in a Typical Year

Cervical spine injuries	9
Disk or discogenic low back conditions	32
Arthrosis (Osteoarthritis) of the thoracolumbar region	4
Miscellaneous skeletal lesions, such as angioma, and vertebral compression	5
Back pain of undetermined origin, functional	1
Total	51

of duty disability or ordinary service retirement. In view of the premium for line of duty disability retirement and certain added income tax advantages, the problem of distinguishing between line-of-duty injuries and non-line of duty injuries, and the results of injury as compared with the effects of age and disease, has been a constant, and at times in superable, problem and challenge to maintain complete fairness to the involved men and the City.

Those retiring for back conditions in the year analyzed are classified in Table II.

It is evident that the major problem is that of disk conditions and injuries including discogenic low back pain and sciatica, without proved disk herniation. This applies to the cervical region equally, as most of the cases there were classified also as discogenic or disk conditions with or without cervical radicular syndromes. Everything said here about the low back refers as well to the cervical region.

Etiology

It is surprising and disturbing that the exact cause of low back pain, and even of the associated sciatic neuralgia, is not known definitively, despite

the frequency of these conditions, and their often severe, prolonged, and permanent disability. Multiple diagnoses have been found recorded in the files of the men suffering from these conditions. These depend on whether the man has been seen or treated by a general practitioner, an internist, an orthopaedist, neurologist, or neurosurgeon, or indeed by a chiropractor or osteopathic physician. They also depend on when the practitioners involved received their basic medical education and whether they have kept up to date. Thus, apart from such obvious conditions as contusions, penetrating wounds, fractures, and dislocations, the major group of these cases had diagnoses such as lumbago, low back pain, low back syndrome, lumbosacral sprain, sacroiliac strain, myofascitis, fibrositis, and myofibrositis. As the condition progresses, with or without reinjury, and time passes, the more severe and disabling conditions gradually are recognized as disk abnormalities (2-6), which chronologically and pathogenetically are based upon fissuring, intradiscal pressure changes, abnormal edema or hydration within the nucleus pulposus, sprain involving the annulus fibrosus and posterior longitudinal ligament, rupture, herniation or protrusion of disk material, degeneration, instability of the posterior intervertebral joints, and secondary osteoarthritis. The structures other than disks which may be basically involved, are the small intervertebral apophyseal joints with their facets, surrounding joint capsules and ligaments (4), and their known tendency to arthrosis, lipping, spurring, hypertrophic change, instability, and subluxation. Both disk lesions and joint lesions have in common actual encroachment on the intraspinal canal and its contents, which include the major nerve roots, local blood vessels and nerves, and ligaments, and which are sometimes superimposed on a congenitally small intervertebral canal (4).

In the earlier stages of evolution of the typical disability the pain is usually low back pain (or cervical pain), in or near the spine, with associated diffuse referred pain at times into the posterior iliac regions, buttocks, hips, even groins or testicles, and down into the lower limbs (or shoulder girdles, upper limbs or cervical sympathetic distribution in the cervical cases). These do not follow a strictly radicular distribution, but are of the type experimentally induced by local injections of hypertonic saline into the various innervated structures of the back (5, 8). However, true sciatica or radicular pain in the distribution of specific nerve roots may supervene with any episode, even the very first, but more often after several, or many attacks of prior low back pain. In the early stages and often for many years, the low back condition and the disability are typically episodic, with intervening periods of apparent normality. This is despite the fact that the underlying anatomic, radiologic, and pathologic abnormalities seem constant and there is no obvious reason for the intermittent nature of the symptoms and disability.

Finally, the condition becomes more persistent, chronic, recurrent and disabling, failing to subside completely between attacks. Involvement of the fibro-osseous envelope (4, 5, 8) surrounding the vertebral canal and its contents at one or more levels becomes evident, including conditions of the

disk, facets of the apophyseal joints, their ligaments, the laminae, the ligamenta flava, pedicles, and vertebral margins. In the early stage these cannot be differentiated from one another so that the exact diagnosis is approximate and the prognosis guarded. They become more definite, only as the course evolves, over a period of months or years or even decades, producing clinical, radiologic, and operative findings which clarify the underlying conditions. Before that stage, much of the diagnosis is guess work and based only on clinical impression. Our problem as physicians is the confirmation of this impression by radiologic or laboratory tests to make a firmer diagnosis on which prophylaxis, treatment, and prognosis can be based.

Apart from the actual fact of an initial injury and the circumstances surrounding its occurrence, many orthopaedists feel that the initial underlying abnormality is some degeneration—chemical, metabolic or mechanical, with alteration of fluid or pressures, within or without an intervertebral disk or disks. This may begin early in life, even in childhood or adolescence, but more often in early adulthood, and may exist in silent form for years until clinical manifestations are triggered by an injury, slight or major. An alteration of intradiscal pressure (6, 8) may cause abnormal stress on the surrounding annulus fibrosus which may give way as a true ligamentous strain, posteriorly, or occasionally, laterally or anteriorly. Disk rupture may even occur in early life into the vertebral bodies above and below. This may become evident later as Schmorl's nodes adjacent to the disks, as the prolapses become detectable by x-ray due to surrounding calcification.

Pain

Nerve fibers are not present in the nucleus pulposus or in the deeper fibers of the annulus fibrosus, or the deeper fibers of the ligamenta flava (8). However, fine nerve fibers believed to carry pain sensation occur in the lumbodorsal fascia, supra and interspinous ligaments, anterior longitudinal ligaments, and vertebral periosteum. The intervertebral joint capsules, outermost layers of the annulus fibrosus, and posterior longitudinal ligaments are richly innervated (8). Injection of the annulus fibrosus and intervertebral joints with hypertonic saline produces the typical pain of the low back syndrome, while injections of the more superficial fascial and fibrous structures produce a different type of local low back pain (8). In later stages, nerves invade the disk along with granulation tissue caused by attempted repair of repeated injuries or mechanical disorders. Increase in intradiscal pressure in the presence of the mechanically or otherwise degenerated nucleus pulposus may be a contributing factor in causing rupture of the annulus and disk protrusion or herniation (8).

Even though the intervertebral disk is the common site of the pathophysiologic mechanism in low back pain, analysis of the patient's symptoms discloses a complex picture marked by great variations in the distribution and severity of pain, and markedly varying degrees of impaired function

(4, 8). Pain may originate also in other elements (ligaments, joints, fasciae, and muscles) involved in the mechanical behavior of the back. A study of 1,000 intervertebral synovial joints at autopsy (8) showed that the upper lumbar intervertebral levels were affected by arthrosis at a younger age than the lower interspaces, but not as young as the cases at the onset of disk lesions. After the age of 45, the arthrotic changes in the lower lumbar levels were more marked and more frequent. Changes in the intervertebral synovial joints appear later than disk degeneration and, chronologically, changes in the synovial joints appear after the patient has already had his first attacks of low back pain, sciatica, or both, so that these joint changes are not the primary cause, but may contribute toward or aggravate later disk degeneration and impaired function.

The direct cause of onset in the firemen is usually traumatic, but very varied in nature and severity. Certain activities of firemen render them prone to this type of back injury eventuating in recurrent low back disability. Most are young and vigorous on entry into the Department, and in prime physical condition, as the less fit are excluded by the testing process of qualification. They continue to work between the ages of 21 and 50, with relatively few above that age, and those chiefly as officers, supervisors, and administrators. They must be ready to perform intermittent heavy work involving frequent and strenuous bending, lifting, and carrying, as well as pushing and pulling, often in awkward, unbalanced positions. As they continue in the work, many change from well-conditioned, physically fit youthful adults to more and more sedentary, poorly-conditioned, flabby-muscled, poor-postured aging individuals. The contrast of long periods of sedentary living, lack of exercise, loss of muscle and ligamentous strength and tone with the need to perform strenuous work at fires in sudden, intermittent irregular bursts or episodes which may be prolonged to many hours or days at a time, is apparent. This tends to produce decompensation of the stability and function of the back, superimposed on whatever underlying congenital or acquired degenerative abnormality may already be present, and clinical symptoms and disability results. Harmon (4) and Hirsch (2, 7, 8) have described in a number of papers the anatomic and pathologic conditions which may underlie such tendency to spinal decompensation. These include such conditions as congenital or acquired stenosis or contraction of the spinal canal (some degree of which may involve one-third of otherwise normal people and be associated with unusually thick neural arches); segmental contraction of the spinal canal; encroachment by advancing osteoarthritis with lippling and spurring, often within the canal; post-traumatic listhetic states, either forward or backward in direction; local diseases of the vertebrae; such soft tissue conditions as giant or ridge-forming disk protrusions, hypertrophic ligamentum flavum, edema and inflammation of ligaments and nerve roots, associated with dynamic changes of posture, motion, and pressure as involved in cough, sneeze, and strain; pseudospondylolisthesis with associated disk degeneration; variations in size, con-

tour, and tropism or plane of the articular facets of the small joints causing variations in size of the lateral pre-articular recesses in which the nerve roots may lie; and various forms of transitional vertebra at the lumbosacral junction. While some of the latter which are bilateral, and thus stable, despite a vestigial disk, are of no consequence, others, unilateral and not contributing to the sacroiliac joint, result in considerable instability and likelihood of disk protrusion in the next most cephalad intervertebral disk.

Some of these findings are detectable by x-ray and other clinical examinations, but many are not until and unless surgical exposure is required and carried out, or the area can be studied anatomically as at autopsy.

Since the men stay in the Fire Department twenty or more years, aging factors gradually increase in importance. With slow degenerative processes very common in the spine in the working span of these age groups, it is often difficult or impossible to separate the effects of trauma from the ordinary wear and tear, and degenerative aspects. Any one episode, though it may last weeks or months, and be followed by prolonged remission of all symptoms, must be viewed against the entire background of the patient's adult life and aging. Deciding what is symptom-producing and what is clinically silent or normal may be extremely difficult even with complete clinical, radiologic, and neurologic study. Even in late stages, when disk degeneration and narrowing, secondary spondylosis, facet subluxation, encroachment on the vertebral canal, and even spondylolisthesis or pseudospondylolisthesis may be present, for long periods even such cases may be clinically silent until an injury, often in line of duty, sometimes trivial, sometimes moderate or severe, triggers the clinically obvious disabling low back disability syndrome. Even activities such as bending over to wash, brush teeth, make a bed, sneeze, cough, tie a shoelace, or put on trousers may start the clinical disability.

Firemen, however, have certain occupational hazards that make them even more vulnerable to low back injuries than other industrial or civilian groups. Thus, handling or pulling or advancing a charged (that is, filled with water under high pressure) hose-line, is a strainful activity involving heavy use of the back, team work, and coordinated activity of several men, especially when it involves climbing ladders, or going up or down stairs at the same time. If one of the men slips or stumbles, or lets go because of smoke or poor visibility, or objects in the way, the remaining men often take the full force of the hose line, and become subject to low back strain or worse. Falls from heights are frequent causes of accidents, with occasional jackknifing and vertebral compression, perhaps accompanied in severe cases by injuries such as spinal cord or nerve root damage, or paraplegia. Building collapses may produce similar injuries either by falls or crushing, if men are buried under heavy masonry debris. Collisions of fire vehicles, with constant pressure to get to the fire as soon as possible, falls from the apparatus in getting on or off in their quick starts, stops, and turns in

heavy traffic, falls due to poor technique while sliding the poles descending from one floor in fire houses to another rapidly, falls over unseen objects and defects in the floors of burning buildings, all may lead to any type of back injury.

Actual fractures of the vertebrae are far less frequent than the ligamentous, muscular, and disk conditions. They are managed by standard methods and do not present too much of a problem except when there is marked spinal cord or nerve root involvement. In the absence of such involvement, such cases often do better than the disk or discogenic or low back syndrome cases unless there is marked compression of a vertebral body or multiple transverse processes are involved.

Automobile accidents and collisions are frequent in the Department. They may cause any type of low back injury or neck injury, including the so-called "whiplash" injury of the neck, in all degrees of severity. Lifting, carrying, pushing, and pulling strains are obviously frequent in firemen's work, with resultant muscular and ligamentous strains and sprains. Such tasks include, besides handling charged lines, moving furniture, machinery, and equipment, breaking through ceilings and walls, clearing debris, and rescuing people from fire premises.

Clinical Classification

1. LOW BACK SYNDROME—ACUTE ONSET

There is a group of cases in which there has been an immediate severe injury with the clinical picture of a severe lumbosacral sprain without any radiologic abnormality detectible by ordinary x-ray studies. These are quite common in the more severe injuries noted above, and the largest problem involving the back in the Fire Department. They vary in their clinical course:

- a. They may recover completely in weeks or months.
- b. They may apparently or temporarily recover, but with a tendency to recur in acute or subacute episodes at greater or lesser intervals. These often are months or years apart, with or without overt reinjury in the later attacks.
- c. They may recover to a certain degree, but incompletely, with residual occasional or persistent low back pain, or sciatic radicular pain, to be endured. Many of the men in the younger age groups, still interested in progressing in their profession, return to full fire duty despite the residual, and continue until and unless more severe recurrences or prolonged exacerbations occur. Others are never able, or are unwilling, to return with such residual symptoms, especially if they have any conscious or subconscious fear of their safety at future fire-fighting.
- d. Not infrequently, as noted in the retirement figures of the test year (Table II), permanent partial disability is deemed to have occurred, and permanent assignment to light duty, or retirement, is necessary.

2. SUBACUTE ONSET

Another group of cases begins with much less trauma and a subacute clinical picture. These injuries may be due to minor lifting, carrying, pulling, or jarring, resulting in the usual mid-low lumbosacral pain extending to either side, often with referred pain in the sacroiliac regions, and minor thigh and leg radiation. Some spasm and spinal tilt may be present. These, also, may last only a week or two and subside. However, many of these, impossible to predict accurately at first, develop recurrences within one or more years, often repeated, even without additional injury, sometimes with repeated minor off or on-duty strains or reinjuries. After a few such episodes, radicular pain may develop and become severe, over-shadowing the back pain, with or without positive objective neurologic findings. The ensuing disability for work may last for many weeks or months. This is the common course of a low lumbar intervertebral disk herniation. It is probable that in this sort of case the first pathologic change is not due to the injury itself but to prior degenerative change within the nucleus pulposus of unknown cause which weakens the disk and makes its ligaments vulnerable even to the minor strains and wear and tear of everyday life, accentuated by the type of work required of firemen (2, 3, 5, 6, 7, 8).

From then on, further weakening and repeated ligamentous damage in repeated episodes may lead to:

a) Full-blown disk herniation syndrome with prolonged disability, often requiring surgery for even palliative relief.

b) Gradual degeneration of a disk with local thinning and instability, as may be detected by stress x-rays of the spine in flexion and extension (14), and by local hypertrophic osteoarthrotic changes. Such radiologically evident degenerative disk changes are late sequelae—often many years after clinical onset—of the repeated low back episodes. Ultimately, in and of themselves, they may result in chronic low back pain and weakness, which is more or less disabling depending on the age, the work the individual is required to perform, and his willingness to continue working and endure the pain although he may be eligible for pensions and other retirement benefits if he cannot work. Such voluntary factors as the imminence of retirement and the possibilities of promotion, and the actual job assignment (officer versus fireman) play a great part in the complaints of disability. Occasionally, if not subject to too much strain, such a degenerated narrowed disk may become spontaneously fused or stabilized, and back symptoms of long duration may disappear. Recurrence or relapse of disability after that may be due to clinical activity or early degeneration of an adjacent disk not obviously involved by x-ray, arising at a later date than the original disk condition.

3. NON-TRAUMATIC ONSET

No known injury may occur at all, but gradually degeneration of one or more disks may take place as previously outlined, herein with repeated

episodes of low back pain and/or sciatica, with the same ultimate result. Undoubtedly, in these cases some metabolic or physicochemical, or mechanical change (2, 5, 8), alters the pressure or elasticity of the nucleus pulposus and renders it unable to withstand the strains of everyday human life. This is often progressive with aging, although not infrequently the changes begin in adolescence or young adult life.

Clinical subvarieties seen occasionally, but less often than the typical low back syndrome cases, include a few upper lumbar disk level cases as part of local spondylosis in the older men. Backache, radicular pain, and disk degeneration may be localized in the upper lumbar region and radiate along nerve roots L1, L2, or L3. These are usually less severe disabilities with a higher frequency of spontaneous remission with or without treatment. However, in the late stages of recurrent cases, in the older age groups, these too may be permanently disabling for fire duty and demand limited service assignment, or retirement.

In the dorsal spine, similar degenerative changes occur occasionally, with a similar long-term outcome. Usually, however, these are noted to be superimposed on old adolescent round back or Scheuermann's vertebral epiphysitis, which may be completely asymptomatic and undetected prior to preemployment radiologic examination at the time of entry of the individual into the Fire Department. The late result is disk degeneration, osteoarthrosis, instability, and clinical decompensation of the back in a fair number of cases.

Gradual cervical disk degeneration at the levels of C5-C6, and C6-C7 is extremely common with increasing age in the apparently normal population in and after the fourth decade, often without injury and without clinically recognizable symptoms (12). Here, too, injuries of varying severity and acuteness of onset may lead to acute stiff necks, radicular pain in the shoulder girdle or upper extremity, or to full-blown herniated disk syndromes with root compression. Many of these are transient and subside in weeks or months with less serious residua than the low back cases, so that the men can tolerate working in spite of residua. However, there is an appreciable number of men who suffer from the same prolonged and permanently disabling chronic degenerative changes in and about the disks after a few, or many, episodes, as the low back cases. Here, too, there is late x-ray evidence of disk narrowing, instability, local hypertrophic change, and reversal of the normal cervical lordosis. The nerve roots may be encroached upon within the spinal canal, in the intervertebral foramina, or adjacent to Luschka's uncovertebral joints, with resultant intractable and disabling cervical radicular syndromes. They can be as refractory to all forms of treatment as the low back cases. They constitute the second most common group of prolonged and permanent disabilities of the spine, and, indeed, of all orthopaedic conditions in the Fire Department.

In the 51 permanent disability cases of a typical year attributable to back or spine conditions, all the above groups are represented. (See Table

II.) Of the 32 cases grouped as disk or discogenic, 15 were definitely diagnosed as disk abnormalities by techniques such as x-ray study, surgical exploration, or neurologic findings. Seventeen had similar clinical histories, episodes, and physical examinations, but had not been definitely proved to be disk herniations or degenerations by the time they were considered to have a permanent partial disability. They were, therefore, called low back syndrome, probably discogenic. General or local osteoarthritis with less evident disk involvement clinically or radiographically accounted for 4 more. Miscellaneous causes of permanent disability classification included compression of vertebrae due to old trauma, congenital defects, angioma of a vertebra, and old adolescent vertebral epiphysitis. In other years, such conditions as Paget's disease of the spine, osteomyelitis, tuberculosis, and neoplasms were also found as causes of permanent disability in firemen, leading to retirement or limited service, but these are much more rare than the causes in Table II. The number of cervical spine cases of all sorts confirms the incidence as next most common to the low back cases.

The low back disk and low back syndrome cases were further analyzed to include age incidence at onset of complaints, age at permanent disability finding, and length of time in the Department (reciprocal to length of time remaining till normal retirement). (Tables III-VI).

TABLE III
Age at Assignment to Limited Service

Total Cases:	32
Age 30-39	8
Age 40-49	15
Age 50-55	6
Age over 55	3

TABLE IV
Time in the Fire Department before Onset of First Episode

Under 10 years	5
10 to 20 years	16
20 years or more	7
Unknown	3

TABLE V
Age at Time of Onset of First Episode

20-29 years	1
30-39 years	8
40-49 years	14
Over 50 years	4
Unknown	4

TABLE VI
Time After Final Episode Until Limited Service

Six months or less	14
Six to twelve months	11
Over twelve months	6

From these tables, the incidence of the conditions discussed above is seen to be chiefly in the men in their second decade in the job, although it could appear occasionally for the first time in earlier or later periods. This correlates with the age of the men at onset, chiefly in their thirties and forties. The older age groups and correspondingly longer times in the Department before onset are heavily weighted by the fact that many firemen of those ages normally retire for completion of service before they are disabled. Therefore, many of those remaining were officers, who can continue to serve until an older age and for longer time in the Department, not being required to do as strenuous physical work as the firemen. The relatively short time from the onset of the final episode until limited service assignment was due to their known prior severe recurrences or prior prolonged back disability histories and high incidence of positive x-ray findings indicating irreversible and incurable pathology.

The cervical spine cases had approximately the same distribution by age and time of onset as the low back cases, but the cases were too few to justify statistical analysis. The generalized osteoarthritis cases were somewhat older than the other back cases at the time of permanent light duty assignment and were much longer in the job when they became symptomatic, indicating the degenerative nature of the disability as compared with the traumatic in the younger men. On the other hand, the miscellaneous skeletal group was disabled either symptomatically or by fortuitous x-ray evidence of a significant lesion at a somewhat earlier age and shorter time in the Department.

Diagnosis

It is not the purpose of this article to discuss this in detail. The various low back syndromes are interchangeable and vary in appearances from attack to attack, depending on the severity, and associated spasm, with or without spinal or pelvic tilt and distortion. The latter is related to the location of the disk lesion laterally or toward the midline, rather than the level of the disk protrusion. Presence of sciatica is detected by the usual history, and physical examination, with emphasis on neurologic findings, including motor, sensory, and reflex findings as well as gait and motion studies.

Certain radiologic and laboratory procedures have been reported to be most accurate in ultimate diagnosis of the exact types of lesion present and their exact location, especially if surgical approach is being considered.

Careful radiographic study of the spine, repeated at intervals, and including such special studies as cephalad oblique and right and left oblique views, stress and motion studies such as lateral flexion and extension views, and cineradiographic studies are very helpful in detection of local levels of pathology, instability, subluxation or local restrictions of motion. Myelography and discography (15) have been used almost exclusively as presurgical methods of final pinpointing of lesions, although they are well known to show false positives and false negatives, rendering their findings somewhat unreliable. In these firemen, even though they were under the direct care and management of their own physicians, including neurologists, neurosurgeons, orthopaedists, as well as general practitioners, chiropractors and osteopaths, none had had discography, which is still not widely accepted as a routine diagnostic measure. This is undoubtedly because many clinically normal patients will show one or more abnormal disks by this technique (12), the abnormality being no different from that found in patients with symptoms. Thus, while discography is an accurate method of ultimate detection and localization of disk pathology, it is inaccurate in locating the area causing the clinical symptoms and disability in many cases. Myelography, if specifically used to locate space encroaching conditions of the vertebral canal, with special reference to disk protrusion, is very helpful, but not so much in routine management as in preoperative pinpointing of the lesion for surgical treatment. Electromyographic study, to localize which roots are involved and thus where the lesion is, or whether one is present, has not been of enough definitive value to warrant general use except again as a confirmatory method, if need for operation has already been indicated.

Prophylaxis

From the viewpoint of the Department, and of the men involved themselves, it would be helpful if those individuals with a tendency to future back degeneration and instability or vulnerability to injury can be pre-selected, and thus eliminated, from the occupational hazards of the job. It is hard to convince an individual who has been rejected because of an x-ray abnormality of the spine before he has had any major symptoms or disability, and who has his heart set on a Fire Department career, that this is proper and just. Nevertheless, some attempt at such preselection is warranted.

Thus, a history of low back sprain of more than transient type, as sometimes available from a previously recorded compensable injury, should disqualify, especially if there have been any complications such as associated radicular pain or spinal tilt. In many cases, however, such history may be unavailable, or concealed. Physical examination is usually not very helpful in the age group seeking admission to the Fire Department. Yet, severe scoliosis, significant increase in the dorsal round back, and marked postural defect, such as sway back and hyperlordosis, should lead to careful evaluation before acceptance or rejection.

Most of the preventive preemployment examinations of the spine used in industry have been radiologic. In most cases this has included routine radiography of the lumbosacral spine or any other part of the spine indicated by the history or physical examination. This has been done in the New York City Fire Department only since March, 1965, as part of the pre-admission medical examination. In the course of the first year, 598 new men were examined, of whom 58 were rejected because of some radiologic abnormality of the back (Table VII).

In some cases, more than one of these defects was found in a single individual, especially the occurrence of disk degeneration, Schmorl's node formation, transitional vertebra and local osteoarthritis in various combinations. Schmorl's node formation represents disk prolapse into an adjacent vertebral body and indicates disk degeneration, though clinically silent in the younger age group.

It is likely that with more detailed radiologic study of the back (not done yet in the Fire Department) more men can be detected who are likely candidates for future crippling back disability. Myelography and discography cannot be used in a preemployment physical examination routinely in view of the hospitalization required and the potential harm that might result as complications in the candidates. Also the pain inflicted and the probability of false positive or negative tests render these procedures inadvisable except as localizing tests where severe disability already exists and surgery may be contemplated.

However, less complicated and dangerous tests might include cineradiography or lateral x-ray examination in full flexion and extension views, in the erect attitude in the cervical region, and in the recumbent, as well as the

TABLE VII
Classification of Spinal Conditions Leading to Rejection

Disk degeneration	23	
Lumbosacral		11
Dorsal		2
Cervical		1
Schmorl's node type		9
Failure of fusion of posterior elements other than slight spina bifida at S1	10	
Unilateral transitional vertebra (sacralization of L5 or lumbarization of S1)	11	
Spondylolisthesis	4	
Old compression fracture,	1	
Apophyseal anomaly and failure of normal development or congenital fusion	1	
Scoliosis, severe	1	
Osteoarthritis	7	
Lumbar		3
Dorsal		1
Cervical		3

erect attitude in the lumbar region. Such study might detect appreciable numbers of hyper- or hypomobile disk levels in the candidates, indicating instability (14), altered pattern of motion—suggesting local spasm or lesion—and gas shadows or calcifications within the disk spaces, all of which might disqualify as suggestive of already established disk degeneration, with its known vulnerability to further injury and disability.

Careful lateral radiography of the lumbosacral spine with measurement of the lumbosacral angle and the weight bearing axis may also be helpful in weeding out future back disability cases. Thus, according to Ferguson (1), the lumbosacral angle may be mechanically unsound in one or both of two ways. The center of gravity of the trunk as represented by a vertical line through the center of the third lumbar body may pass anterior to the sacrum, sometimes by as much as two inches. Insofar as this line is anterior to the sacrum, a certain portion of the weight is not borne by bone but by muscles or ligaments which are liable to strain. Or, if the plane of the articular surface of the first sacral vertebra is too far from the horizontal, shearing stresses may be set up making the muscles and ligaments subject to strain. When this surface is as much as 42° from the horizontal axis of the patient, the strains are of some importance; when the angle is 47° they are said to be a menace; and when the angle is 52° or more, the stresses are severe. For proper evaluation, Ferguson (1) believed that careful positioning in the patient's usual relaxed posture in recumbency was necessary to prevent false readings by protective reaction in the standing attitude. He also felt that in lateral views in flexion and extension, motion of the spinous processes of L5 and S1 more than one-half inch relative to each other, indicated instability.

It must be realized that these criteria are not universally accepted and that in an otherwise healthy, symptomless young adult it might be difficult to justify rejection unless the features aforementioned indicated were extreme, rather than borderline of normal. It is for this reason and because of the difficulty of obtaining perfect radiographs perfectly positioned in a large number of men being rapidly processed that these more detailed radiographic studies have not yet been incorporated into the preemployment examinations. The criteria actually used (Table VII) are more definite and less controversial. Even in those cases, there is often objection by the candidates and by physicians consulted by them, who state that all of these conditions are compatible with perfect health and that they should not automatically be rejected therefore.

A second form of prophylaxis used in the Fire Department is by instruction of all firemen in the proper use of heavy apparatus in fire-fighting situations, such as charged hose lines, in situations where heavy material or debris has to be lifted or moved in the proper posture of lifting and carrying, and in the need to have adequate and coordinated assistance for the more strenuous tasks. Several tabloid charts giving instruction in proper positioning of the back at work and in everyday living are now available.

including rules for proper lifting, bending, and carrying. One such is noted in Sheets 1A and 1B. These often include instruction in postural low back exercise as treatment. Regular performance of these is of prophylactic value in lowering the incidence of back injuries.

A. Exercises for low back pain

General Information:

Don't overdo exercising, especially in the beginning. Start by trying the movements slowly and carefully. Don't be alarmed if the exercises cause some mild discomfort which lasts a few minutes. But if pain is more than mild and lasts more than 15 or 20 minutes, stop and do no further exercises until you see your doctor.

Do the exercises on a hard surface covered with a thin mat or heavy blanket. Put a pillow under your neck if it makes you more comfortable. Always start your exercises slowly--and in the order marked--to allow muscles to loosen up gradually. Heat treatments just before you start can help relax tight muscles. Follow the instructions carefully, it will be well worth the effort.

Do exercises marked (X)

in numerical order

for ____ minutes

____ times a day.

Take the medication

prescribed for you

____ times daily

for _____

1



Lie on your back with your arms above your head and your knees bent. Now move one knee as far as you can toward your chest and at the same time straighten out the other leg. Go back to the original position with both knees bent, and repeat the movements, switching legs. Relax and repeat the exercise.



2



Lie on your back with your arms at your sides and your knees bent. Now bring your knees up to your chest and with your hands clasped pull your knees toward your chest. Hold for a count of 10, keeping your knees together and your shoulders flat on the mat. Repeat the pulling and holding movement three times. Relax and repeat the exercise.



3



Relax with your arms above your head and your knees bent. Now tighten the muscles of your lower abdomen and your buttocks at the same time so as to flatten your back against the mat. This is the flat back position. Hold the position for a count of 10. Relax and repeat the exercise.



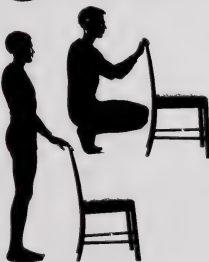
4

Sit on a hard chair. Let your body drop until your head is down between your knees. Pull your body back up into a sitting position while tightening your abdominal muscles. Relax and repeat the exercise.



5

Stand erect while holding onto a table or chair. Squat down, straighten up again, relax and repeat the exercise.



B. How to get along with your back

Sitting: Use a hard chair and put your spine up against it; try and keep one or both knees higher than your hips. A small stool is helpful here. For short rest periods, a contour chair offers excellent support.

Standing: Try to stand with your lower back flat. When you work standing up, use a footrest to help relieve swayback. Never lean forward without bending your knees. Ladies take note: shoes with moderate heels strain the back less than those with high spike heels.



Sleeping: Sleep on a firm mattress; put a bedboard (3/4" plywood) under a soft mattress. Do not sleep on your stomach. If you sleep on your back, put a pillow under your knees. If you sleep on your side keep your legs bent at the knees and at the hips.



Driving: Get a hard seat for your automobile and sit close enough to the wheel while driving so that your legs are not fully extended when you work the pedals.

Lifting: Make sure you lift properly. Bend your knees and use your leg muscles to lift. Avoid sudden movements. Try not to lift anything heavy over your head.



Working: Don't overwork yourself. If you can, change from one job to another before you feel fatigued. If you work at a desk all day, get up and move around whenever you get the chance.

Exercise: Get regular exercise (walking, swimming, etc.) once your backache is gone. But start slowly to give your muscles a chance to warm up and loosen before attempting anything strenuous.

See your doctor: If your back acts up, see your doctor, don't wait until your condition gets severe.

McNEIL LABORATORIES, INC., Fort Washington, Pennsylvania

Sheet 1B

Of course, training in avoiding all the types of accidents to which firemen are especially subject is also helpful in preventing back disability. This would include accident prevention training, proper conduct in fire buildings to avoid falls and collapses, in fire apparatus, to avoid collisions, by use of safety belts and the like, and proper technique in sliding the pole.

Treatment

Treatment has not been effective in eliminating severe and chronic low back and other spinal disabilities. In the firemen, as in civilian groups, this has comprised many modalities. These include osteopathic and chiropractic manipulation, sought by the men as they become disappointed with medical or orthopaedic management; various drug therapies such as analgesics, antispasmodics and muscle relaxants; orthopaedic measures such as varying degrees and duration of bed rest in suitable postures; physical therapy of all sorts; support by corsets, and belts and braces. Prolonged bed rest, avoidance of occupational and other strain, traction, heat modalities, injections of trigger points of pain with local anesthetics and steroids, low back exercises and even surgical intervention in the form of disk removal or stabilization by fusion have failed in many of the more stubborn cases. No therapy, or almost any of the above measures, may be successful in the younger age groups, anxious to return to work to resume their careers, especially if accompanied by adequate periods of rest and avoidance of strain. However, as the men become older, with recurrences, and as they approach retirement, when degenerative processes become more and more important in the clinical picture, the same therapy proves incompletely successful and fails to rehabilitate them to the degree required for normal fire-fighting duties. Operative intervention—by surgeons of the firemen's choice—has usually been reserved for the most severely disabled with prolonged crippling, and has been done by leading neurosurgeons and/or orthopaedists. Nevertheless, very few of the few men treated surgically have returned to full fire duty even temporarily. Practically none injured in line of duty has even attempted to return to such duty. Occasional young individuals who had sustained the back condition in non-line of duty situations have returned to regular duty for several years. They, too, after a time, have suffered further back episodes with spinal decompensation, so that permanent limited service and retirement have been the outcome, often from minor subsequent line of duty recurrences. It has, therefore, been policy, with rare exceptions, that those men surgically treated are considered permanently partially disabled for fire duty and are not urged or permitted to return to such work. Apparently the intricate mechanism of the human back cannot yet be treated surgically with complete restitution of functional capacity to normal. This is consistent with findings of other surgeons (9, 11) in various series reported in the orthopaedic and neurosurgical literature, if they are carefully studied, and followed long enough to get the ultimate results. Some handicap nearly always persists, even though the severe symptoms, such as acute sciatica, may be eliminated, and low back disability improve. Many of the patients are so grateful for the relief of severe radicular pain or backache that they pay little attention to the minor residual aches and pains. However, it is precisely these residua, and sometimes, more major residua and recurrences, that render the firemen

unable to return to their regular duties. Knowledge of this has resulted in the refusal of many of the men to undergo surgery in the chronic category of low back case unless severely and totally disabled so that they cannot do even light work, or be able to enjoy life. They frequently state that they know of someone with similar conditions who has been inadequately, if at all, improved by surgical intervention.

Summary

The entire background and pathogenesis of the most common types of disabling back conditions as they apply to occupational disabilities of men serving in the New York City Fire Department have been reviewed. The incidence of the various types of disability, their causes and evolution, have been discussed. The time of occurrence in relation to age and service in the Department have been described. It is obvious that a great deal more information may be obtained along those lines if a prospective study over a long period of time could be undertaken, rather than a retrospective study based on frequently inadequate records. Statistics as to economic loss from loss of man-hours of work and premature, service-connected or other retirements, with the associated increased pension expense should be kept accurately, to emphasize the importance of the problem. Classification of the various types of back conditions leading to chronic and severe disability has indicated that the low back syndrome leading to disk protrusion and/or disk degeneration, and secondary instability, arthrosis, and radicular involvement is the most common type. Prevention by preemployment selection, adequate job training and preparation, and management by proper conditioning and exercise to minimize the numbers of disabled men and the number and severity of recurrences is most important in solving the problem. Measures currently used in this type of preemployment examination to weed out men prone to future disability, although obviously crude and uncertain, may be improved in the future as better diagnostic modalities become available and are used routinely. Finally, it has been indicated that there is no magic treatment adequate for all cases, and that surgery, not being curative, should truly be a last resort for severe disability preventing all normal activities of everyday living with the knowledge that, even if dramatically improved, the men will usually not be rehabilitated for the normal duties of a fireman.

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Radical Local Surgery in Diabetic Gangrene

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Minor injuries, tinea pedis, or the continual trauma due to a plantar callosity frequently lead to foot infections in the diabetic. The natural history of this condition shows that unless halted by early and adequate treatment, such infections will often spread upwards rapidly to produce extensive abscess formation and tissue necrosis of several toes and of the distal part of the foot. Severe toxemia and diabetic acidosis frequently follow, and may necessitate emergency guillotine amputation as a life-saving measure (1, 2). In order to prevent risk to life and minimize limb loss, early surgical drainage with removal of all necrotic tissue is essential, as antibiotics and other supportive treatment are usually not able to contain this type of gangrenous process (3, 4, 5).

This report describes the management of 24 consecutive diabetic patients with infected gangrene of toes and forefoot, observed on the Peripheral Vascular Disease Service of this hospital between July 1964 and December 1965. In all cases a good popliteal pulse, and some one or other of the ankle pulses were present. On this circulatory basis the diagnosis was made on the characteristic appearance of wet, infected gangrene, the presence of redness and swelling in the more proximal parts of the extremity, and signs of systemic disturbance manifested by fever, leukocytosis, and a temporarily increased demand for insulin. All our patients demonstrated at least three of these features. We are not reporting here on patients with dry, ischemic gangrene as primary local amputation plays no part in their treatment, and all efforts must be directed at improving the distal blood supply by sympathectomy or arterial reconstruction. This group will be included in a subsequent report from this department.

Treatment in all patients comprised correction of the metabolic disturbance, the administration of suitable antibiotics, and immediate radical local debridement. Surgery must include removal of all dead and infected tissue, including bones and tendons. Normal anatomical and functional landmarks must be ignored, and pus and slough removed until healthy, bleeding structures are exposed. The wound is never closed primarily, but healing by granulation is encouraged with local measures, and sometimes speeded by the later application of a skin graft.

Results

Treatment failed in five patients. Four required eventual below-knee amputation. One patient signed out of the hospital against medical advice with an unhealed wound of the foot. (Table I.)

From The Mount Sinai Hospital Services City Hospital Center at Elmhurst, New York.

TABLE I
Failed Treatment

B/K amputation	4
Unhealed wound	1
Total failed pts.	5

TABLE II
Successful Treatment

Healed by secondary intention	12
Healed with skin graft	7
Total healed pts.	19

In 19 patients radical local surgery was followed by the appearance of satisfactory granulations, and healing by secondary intention in 12. The remaining 7 patients had a split thickness skin graft applied to the granulating wound, with satisfactory healing in all cases. (Table II.) The most commonly used procedure was based on the excision of one or more toes, and the head and distal portion of the shaft of their accompanying metatarsal bone. All operations were performed under general or spinal anesthetic, without mortality (Figs. 1-7).

Discussion

Gangrene in the diabetic generally falls into one of two distinct groups. Ischemia due to major limb vessel occlusion may be the principal cause. Here the affected parts are dry and shrunken. Popliteal and ankle pulses are usually absent. The necrotic process is of several weeks' duration and there is no derangement of the diabetic state. Such patients should be considered for arterial reconstruction where feasible, as a major amputation is commonly the only alternative (6, 7).

The group of patients reported here demonstrates the second type of clinical presentation, where florid, wet gangrene, abscess formation, and deep tissue necrosis are the principal local features. Neuropathy, the metabolic disturbance and lesser resistance of the diabetic to infection are the principal predisposing factors. Ischemia is of secondary importance, affecting only the small vessels of calf and foot (4, 8). The final local precipitating cause is frequently accidental trauma, an injury while cutting the toe nails, fungus infection, the presence of a thick plantar callus, or injudicious attempts to remove it (3). Provided a good popliteal pulse is palpable, we believe that the above described clinical picture demands drainage and debridement as the primary form of treatment.

The key to the correct management of this condition lies in accurate clinical diagnosis (3, 4, 9). Careful evaluation of the arterial circulation and



FIG. 1. Case #15. Two weeks after radical debridement.



FIG. 2. Case #15. Skin graft applied three weeks after primary surgery. Photograph two months after skin graft.



FIG. 3. Case #16. Auto-amputation of fifth toe, gangrene and deep plantar abscess.

FIG. 4. Case #16. Radical local excision completed.

FIG. 5. Case #16. Healed skin graft three months later.

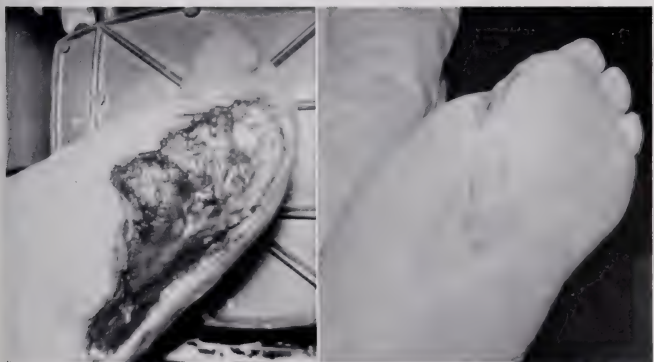


FIG. 6. Case #19. Three weeks after excision of first and second toes and metatarsal heads.

FIG. 7. Completely healed one month later.

clinical appearance of the endangered limb provide the basis for rational treatment as previously outlined. We have performed femoral arteriography on some patients to confirm the distribution of arterial occlusions. It must be stressed, however, that this is by no means essential, and that any delay in waiting for the performance of an arteriogram is unwarranted, and possibly harmful. There are many diabetic patients who have chronic, superficial, and indolent ulcers on the toes, or a penetrating ulcer on the sole of the foot, which have been present for weeks or months. The treatment of these lesions is conservative, and is based on bed rest, local applications, the judicious use of systemic antibiotics, and long-term evaluation of the need for sympathectomy or arterial reconstruction. In some patients a minor disability is best accepted, and provided for by supplying appropriate footwear and advising on other purely local measures to redistribute pressure on the foot. However, once the diagnosis of wet gangrene of any region in the anterior half of the foot is made, and the clinical picture confirmed by the presence of at least the popliteal pulse, the diabetes must be balanced as quickly as possible, fluid deficits corrected by intravenous infusions, and immediate arrangements made for surgery. Antibiotics to control common infecting organisms must be started at the same time, after adequate specimens for bacterial culture have been taken. The temptation to use local blunt and sharp debridement without anesthesia must be resisted because this almost invariably leads to inadequate drainage, and encourages proximal spread of pus and tissue destruction. The timing and adequacy of operation will determine the survival of a useful limb. We have tried to apply the principles presented by McKittrick et al (10) regarding the value of primary transmetatarsal amputation for this condition. All the patients described here had such marked evidence of local inflammation that we felt primary definitive surgery to be unwise, and preferred to concentrate on immediate adequate drainage and debridement in order to encourage rapid resolution of toxemia and the inflammatory process. We were ourselves surprised and gratified in the earlier cases that the lesions went on to healing by second intention with such regularity, that we decided to rely on this approach entirely in all patients where clinical signs seemed to preclude any other form of therapy. We have found that after the radical local removal of all infected, necrotic, and ischemic tissue good granulations cover the wound within seven to ten days, and this can then be allowed to heal by secondary intention, or covered with a fairly thick split thickness skin graft. Notwithstanding the often irregular outline of the remaining foot, the functional result is satisfactory, and all our patients treated successfully in this fashion walk on the healed leg (4). No special appliances have been provided other than the padding of the empty part of the shoe with cotton or sponge rubber.

Summary

Twenty-four consecutive patients with infected, diabetic gangrene are reported on. The keystone of treatment was early radical local surgery, in

the hope of preventing the upward spread of infection and tissue necrosis, and of saving a useful extremity. A major amputation was prevented in nineteen patients, who are now walking on the previously gangrenous limb.

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Intraperitoneal Hemorrhage as a Complication of Acute Ruptured Cholecystitis

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The usual complications of cholelithiasis are hydrops, empyema, gangrene, perforation, choledocholithiasis with or without common duct obstruction, and pancreatitis. Massive intraperitoneal bleeding in acute perforated cholecystitis with cholelithiasis is a rare complication. A total of 27 cases have appeared in the English literature. Twenty-four of these were treated surgically with recovery in sixteen. The purpose of this paper is to add another case to the reported literature.

Case Report

(M.W. #390,365.) A 66 year old man was admitted to the City Hospital Center at Elmhurst, New York, with the chief complaint of abdominal pain and persistent vomiting. His illness started two days prior to admission with pain in the epigastrium and right upper abdominal quadrant. The pain was dull, constant, and radiated to the back and right shoulder blades. After the onset of pain, the patient vomited frank bile a few times. The following day, the pain was more severe and generalized to the entire abdomen; the vomiting became more frequent and uncontrollable. Failure of an enema to bring relief brought the patient to the emergency room.

The patient had had a left renal cyst removed several years ago. An umbilical hernia of 3 to 4 cm in size, reducible and asymptomatic, had been present for a number of years. No history of weight loss, loss of appetite, fatty food intolerance, or recent trauma could be elicited. Bowel movements had been regular except for the previous two days. The patient had had difficulty in urination with dysuria and nocturia for the past few months, and had not voided for 12 hours prior to admission. There was no previous serious medical illness.

The patient was a middle-aged obese white man in acute distress with blood pressure 100/80. The pulse rate was 120 beats/min and the respiratory rate 20/min. The skin was clammy. The conjunctiva were pale and the pupils reacted normally to light and accommodation. The trachea was at the midline. No supraclavicular or axillary lymphadenopathy was felt. The chest expanded equally on respiration. Palpation, percussion and auscultation did not reveal abnormal findings. The heart had a regular rhythm with frequency of 110 beats/min and an apical beat in the left fifth intercostal space. No murmurs were audible. The abdomen was slightly distended. A small umbilical hernia 3 by 4 cm in diameter was reducible and nontender; there were no inguinal hernias visible or palpable. There was a scar in the left lumbar region due to previous operation for renal cyst removal. The abdominal wall was rigid and diffusely tender. The tenderness was more marked in the right abdominal quadrants and maximal in the right upper quadrant. Liver, spleen, and kidney could not be palpated. Bowel sounds were not clearly identifiable. The rectum was empty and nontender; the prostate uniformly enlarged and soft. No rectal masses were palpable.

Laboratory studies on admission disclosed the following values: hemoglobin, 10.9 gm/100 cc; hematocrit, 33%; white blood cell count (wbc), 20,600 with polymorphonuclears 86%, lymphocytes 10%, and 4% monocytes; serum sodium, 144 mEq; serum po-

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tassium, 4.1 mEq; chloride, 109 mEq; carbon dioxide, 24 mEq; blood sugar, 160 mg/100 cc; blood urea nitrogen (BUN), 26 mg/100 cc; serum amylase, 59 King-Armstrong units. A catheter was inserted and only 50 ml of urine was obtained. Urinalysis showed a specific gravity of 1.020. There was a trace of albumin in the urine, wbc was 8 to 12 per high power field and RBC, 20 to 35 high power field.

On radiologic examination, there was no air in the small bowel loops. Gas was seen in the right colon as well as in the left colon but there was none in the transverse colon. There was haziness of both psoas shadows and a suggestion of a mass in the right gutter displacing the gut medially. A paracentesis revealed frank blood in both lower quadrants of the abdomen. A spontaneous pathological rupture of the liver or a ruptured bleeding cholecystitis appeared to be the most likely disease which could account for the symptoms and signs of the acute right upper quadrant peritonitis and of the hemoperitoneum. After a brief interval in which blood and fluids were replaced, the patient underwent exploratory laparotomy through a midline incision.

The peritoneal cavity contained over two liters of blood. After this was aspirated a large acutely inflamed gallbladder could be seen with a laceration approximately 2 by 3 cm in diameter at the fundus, from which blood was leaking into the abdomen. Palpation of the gallbladder revealed a large stone impacted in Hartman's pouch. The anterior wall of the gallbladder was split open and the stone removed. A large ramus of the cystic artery could be seen freely bleeding in the bed of the removed stone. A large hematoma was also present extending from the hilum of the liver to the mesocolon, elevating and compressing the second and third portions of the duodenum.

The cystic artery was dissected up to its origin from the hepatic artery and was ligated at this point. The gallbladder was then removed. The common duct appeared to be normal in size and no stone could be palpated within it. However, a choledochotomy was performed to rule out other possible causes of hemobilia. Clear bile was found in the common duct and neither stone nor obstruction was encountered. A T-tube was inserted into the common duct and the liver bed was drained. Histologic examination revealed acute cholecystitis with cholelithiasis and perforation of gallbladder. The postoperative course was uneventful. On the tenth day, after cholangiogram failed to reveal any filling defect in the common duct, the T-tube was removed and the patient was transferred to the urologic service for prostatectomy.

Comment

Intraperitoneal hemorrhage as a result of ruptured gallbladder was first described by Leared in 1858 (1) as an autopsy finding. Schnyder (2) reported a similar case in 1915. In 1921 Gjellerup (3) recorded the first successful case with recovery (after surgery). Waters (4) in 1926, Wyse (5) in 1934, Bartlett and Bartlett (6) in 1936 and Sanders (7) in 1937 reported similar cases. Mailer in 1939 collected five cases from the literature and added one of his own (8). Hardy and Spelman (9) in 1947, Fitts et al (10) in 1951, Howard et al (11) in 1952, Cohen et al (12) in 1953, Griffith (13) in 1954, Mason (14) in 1957, Rayercroft (15) in 1960, and Leaverton (16) in 1966 reviewed similar cases. To date, 27 cases of intraperitoneal hemorrhage due to ruptured gallbladder have been documented in the world literature. Three of the early cases were discovered at autopsy; 24 patients were subjected to surgery. Of these, 16 recovered and 8 died following surgery. The present is the 28th published case. Table I summarizes the data of all previously published cases. Hemoperitoneum as a result of rupture of the gallbladder is obviously a rare complication. Much more frequently, hemorrhage from the gallbladder flows through

TABLE I

No.	Author	Year	Age	Sex	Duration of Symptoms	Interval between Operation and Admission	Operative Finding	Operation	Result	Cause of Hemorrhage	Autopsy Finding
1.	Leard (1)	1858	22	M						No vessel could be identified	Death on 13th day of illness; 2 quarts of blood in the peritoneal cavity; ruptured gallbladder; stone in common duct
2.	Schnyder (2)	1915	72	M						Gall stone (stone)	Death after 2 days; blood in peritoneal cavity; perforation 4-5 cm in gallbladder
3.	Gjellerup (3)	1921	72	F			Free blood, 1 liter single stone 15 cm X 4 cm, perforation of gallbladder	Cholecystectomy	Recovered	Gall stone	
4.	Waters (4)	1926	63	F			Free blood, perforation of gallbladder neck, 10 stones in pelvis, 200 in gallbladder, tear in cystic artery	Cholecystectomy	Recovered	Gall stone	
5.	Vest (45)	1933	56	M	10 days	Immediate	Blood, necrotic material and pus, no explanation and cause of hemorrhage	Drainage of abscess cavity	Died	Intense inflammation and gangrene	Gallbladder perforated in 2 large areas

6.	Wyse (5)	1934	79	M	6 days	Not operated upon				Blood in peritoneal cavity, several stones in gallbladder and common bile duct, perforation inferior surface gallbladder
7.	Bartlett and Bartlett (6)	1936	65	F	2 days	Free blood, 100 stones, perforation	Cholecystectomy and packing	Died	Stones; hypertension	
8.	Sanders (7)	1937	45	M	48 hours	Large blood clot under liver, perforation in fundus	Cholecystectomy	Died due to nephritis		
9.	Mailer (8)	1939	65	M	1 week	Free blood, gallbladder perforated 1", single large stone	Cholecystectomy through the rent	Died	Gall stones with circulatory changes	Entire wall of gallbladder had hemorrhage, infarct appearance more of circulatory disturbances
10.	Hardy and Spellman (9)	1947	52	F	2½ days	Blood and bile, single stone, perforation in the distal third of gallbladder, liver laceration	Cholecystectomy	Recovered	Stone with inflammation	

TABLE I—Continued

No.	Author	Year	Age	Sex	Duration of Symptoms	Interval between Operation and Admission	Operative Finding	Operation	Result	Cause of Hemorrhage	Autopsy Finding
11.	Hammer (47)	1950	81	M			Rupture of the gall-bladder in fundus, chronic ulceration and cholecystitis		Died	Impacted stone with increased intravesical pressure	Chronic ulcerous cholecystitis and rent in gall-bladder in neck of fundus, gall stone impacted in the ampulla of Vater
12.	Fitts and Demuth (10)	1951	66	M	32 hours	5 hours	Blood, rupture gall-bladder in fundus, 2 stones	Cholecystectomy, splenectomy	Died	Gall stones and hypertension	
13.	Fitts and Demuth (10)	1951	71	F	48 hours		Free blood, laceration in fundus of gall-bladder, large stone	Cholecystotomy	Recovered	Gall stones and hypertension	

14.	Howard and Griffin (11)	1952	54	F	20 hours		Free blood, multiple stones, calcium in cystic duct, rupture gallbladder	Chole- cys- tec- tomy	Recov- ered	Hemor- rhage from branch of cystic artery, hyper- tension and gall stone
15.	Cohen, W. et al (12)	1953	58	F	3 days	7 days	Blood and bile, perfor- ation in the fundus	Chole- cys- tec- tomy	Recov- ered	Intense inflam- mation and hy- per- tension
16.	Griffith and Bogardus (13)	1954	60	M	6 days	36 hours	Blood in peritoneal cavity, rupture gall- bladder with acute inflammation, no stones	Removal of fun- dus of gall bladder and pack- ing	Recov- ered	Intense inflam- mation
17.	Erfors (43)	1954	65	F			4 cm size rupture in the fundus of the gall- bladder, diffuse bleeding		Recov- ered	Acute chole- cystitis

TABLE I—*Continued*

No.	Author	Year	Age	Sex	Duration of Symptoms	Interval between Operation and Admission	Operative Finding	Operation	Result	Cause of Hemorrhage	Autopsy Finding
18.	Erfors (43)	1954	65	M			Diffuse bleeding, gallbladder perforation extending into liver parenchyma		Died	Acute and chronic inflammation with severe circulatory impairment	
19.	Erfors (43)	1954	59	M			4 cm long rupture into gallbladder mucosa with hemorrhage from cystic artery		Recovered	Acute hemorrhagic cholecystitis	
20.	Erfors (43)	1954	85	M			2½ cm long perforation near the liver bed		Died		
21.	Massie et al (46)	1957	66	F	2 days	Immediate	Blood in peritoneal cavity, perforation at the fundus, multiple stones	Cholecystectomy	Recovered	Inflammation and stones	
22.	Mason et al (14)	1957	43	M	Several hours		Free blood, perforation midportion, gall stones, bleeding cystic artery	Cholecystectomy	Recovered	Intense inflammation, gall stone	
23.	Raycroft (15)	1960	79	F		3 days	Blood, perforation in the ampulla, single stone	Cholecystectomy	Recovered	Stone	

24.	Raycroft (15)	1960	57	F	36 hours	Blood, gangrenous area in gallbladder, bleed- ing from cystic artery	Chole- cys- tec- tomy Closure of per- fora- tion	Recov- ered	Hyperten- sion, stones
25.	Wajda, Z. Lewicki, K. (48)	1962	40	F	3 days	Blood in peritoneal cavity, gallbladder perforation, 1 cm opening closed by impacted stone		Recov- ered	
26.	Leaverton (16)	1966	57	F	7 days Few hours	Free blood, large hole in medial side of gall- bladder, no stones	Chole- cys- tec- tomy	Recov- ered	Inflamma- tion, hy- per- tension
27.	Bervar, M. et al (50)	1964	50	M	3 days	Stones in gallbladder, perforation at fundus	Chole- cys- tec- tomy	Recov- ered	
28.	Naqvi et al	1967	66	M	Imme- diate 2 days	2 liters of blood in per- itoneal cavity, per- foration at the mid- fundus, acutely in- flamed gallbladder	Chole- cys- tec- tomy, common bile duct explo- ration	Recov- ered	Acute in- flamma- tion and stone

the biliary ducts and manifests itself as melena or hematemesis. Bleeding might also remain confined to the gallbladder, resulting in hemocholecyst.

Several causes of intracholecystic bleeding have been described: (1) Cholelithiasis; (2) Vascular disorders (a. hypertension, b. arteriosclerosis, c. aneurysm of cystic or hepatic artery); (3) Benign and malignant tumor of gallbladder; (4) Islands of heterotopic gastrointestinal mucosa with peptic ulceration.

Gallstones are probably the most common cause of hemorrhage into the gallbladder because of their mechanical irritation and also due to the inflammatory changes in the mucosa with which biliary calculi are often associated (17).

The operative findings in our patient suggest the following sequence of events: (1) lodgment of the large stone in the infundibulum of the gallbladder with consequent acute obstructive cholecystitis; (2) pressure necrosis in the gallbladder wall with resultant erosion into the cystic artery; (3) hemorrhage into the gallbladder cavity with increased intraluminal tension leading to rupture; (4) hemoperitoneum and acute peritonitis and (5) simultaneous formation of a large hematoma around the common duct, the descending duodenum and transverse mesocolon. The compression of the duodenum produced a high intestinal obstruction and explains the uncontrollable vomiting which developed on the second day of the illness.

The signs of the peritonitis usually mask the signs of hemorrhage, making preoperative diagnosis rare among the reported cases. Howard et al (11) based a correct preoperative diagnosis on the combination of increasing signs of cholecystitis and shock due to continued blood loss.

In our case, the initial impression was that of an acute inflammatory upper abdominal condition and paracentesis was performed to differentiate acute cholecystitis from acute pancreatitis. The withdrawal of frank blood was unexpected and dictated consideration of all the possible causes of spontaneous hemoperitoneum.

In addition to trauma, the causes of hemoperitoneum are many. In a series of 129 cases, Ellis et al (18) reported a majority of the cases were due to gynecological disorders. Spontaneous rupture of the spleen and liver have been reported (19-22). A few cases of ruptured liver were due to primary and secondary carcinoma (23-26). Splenic rupture occurs in erythroblastosis fetalis, syphilis, and leukemia (29) in the newborn (28). Malaria and infectious mononucleosis (29) are some common causes of rupture of the spleen. Rupture of the large bowel (30-32) also has been reported in literature as a cause of intraperitoneal hemorrhage. Hemoperitoneum due to vascular causes, i.e., aortic aneurysm, aneurysm of splenic (33, 34), hepatic (35, 36), gastric (37) and superior mesenteric and pancreatoduodenal (38) artery have been recorded. Hypertension and arteriosclerosis may be contributing factors in some of these cases. Hemorrhage due to long-term anticoagulant therapy has been reviewed by Perez (39), Pearson (40, 41) and Mendelsohn (42). In spite of the above etiologies, there still remain a few cases where hemorrhage is unexplained at laparotomy.

Intracholecystitis hemorrhage can lead to hemoperitoneum when the bleeding is from an artery and the cystic duct is blocked, since the increased tension is likely to rupture the bladder. In our case, the diagnosis of hemoperitoneum with ruptured gallbladder was considered as a likely possibility because of the absence of pathological conditions predisposing to hemoperitoneum and because of the predominant inflammatory peritoneal signs. The second possibility was rupture of the liver. Undoubtedly, the correct diagnosis was suggested only because a peritoneal tap had been performed for diagnostic purposes, but could be made with certainty only after exploratory laparotomy.

Summary

An unusual case of ruptured gallbladder with intraperitoneal hemorrhage is presented. The preoperative diagnosis was tentatively made on the basis of results from needle paracentesis and of the signs and symptoms of acute peritonitis of the right upper quadrant. The patient underwent emergency operation and recovered.

A total of 27 similar cases have been collected in the literature. Cholecystic bleeding with perforation can be a cause of hemoperitoneum and should be considered in the differential diagnosis of spontaneous hemoperitoneum especially in the adult male and when signs of acute peritonitis are present.

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Minimal Legg-Calve-Perthes Disease

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In the course of extensive study of Legg-Calve-Perthes disease, a group of patients was discovered who exhibited roentgenographic findings of mild to minimal surface contour indentations of the involved proximal femoral epiphysis (Fig. 1). These patients had sought medical counsel because of symptoms of limp and/or pain in the hip or knee of the affected side.

The x-ray change consisted of single surface indentations either centrally or somewhat laterally situated, usually seen in both anterior-posterior and lateral projections but often best visualized in only one view (Fig. 2). Sometimes there were several indentations of the surface becoming contiguous to produce a scalloped appearance (Fig. 3). These roentgenographic alterations progressed along two possible avenues. In the first instance, there was no worsening of the surface irregularity after its identification but only gradual restoration to an almost normal state in a varying period of time. In the second variety, the surface alterations developed short subchondral expansions into the femoral nucleus which continued to maintain an approximate outline of its original form (Fig. 4). Here, also, the healing process went on ultimately to restore the femoral head to an almost normal appearance. The changes described above were in distinct contrast to the accustomed *classical* sequence of progressive fragmentation, reabsorption, and reconstruction of the proximal femoral epiphysis with resulting deformity in epiphyseal broadening and diminution in height.

The basis of this report is furnished by 15 cases (Fig. 5) derived from almost 300 patients with Legg-Calve-Perthes disease. There are 12 males and 3 females in the group which conforms to the usual statistical incidence of 4 males to 1 female in most published Legg-Calve-Perthes series. Ten of the patients have bilateral involvements and five have unilateral changes. This higher incidence of bilaterality (66.2/3%) is at variance with the much lower frequency of bilateral disease in classical Legg-Calve-Perthes (less than 15%). Mose (6) in reviewing the literature found the bilateral incidence mostly to be below 15% with his own series showing only 8%.

The overall average age for the entire group was 4.8 years. In Legg-Calve-Perthes disease of all severities the average age tends to be slightly higher, falling usually in the 5 to 6 year age range.

In a previous publication (5), similar femoral head surface changes were reported in the *asymptomatic, apparently uninvolved hip* in 33 children under treatment for classical unilateral Legg-Calve-Perthes disease. Those cases were regarded to show an "abortive" variety of Legg-Calve-Perthes disease.

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FIG. 1. This 3 year old girl shows slightly scalloped surface irregularity of the left femoral head. The defect persisted for 18 months. The final outline and trabecular texture returned to normal.



FIG. 2. This patient has a minimal lesion of the left femoral head. It is centrally placed in both AP and lateral projections. It did not disappear for 14 months.

The significant difference between the earlier report and the present one is that the minimal hip joint changes on x-ray now are associated with a clinical complement of pain, limp, and hip joint restriction of movement. Usually a short period of restriction of activity suffices to control the symptoms and also permits subsidence of limitation of motion. Treatment is pursued on the basis of the x-ray findings just as it is in most instances of classical Legg-Calve-Perthes disease.

In the previous report (5), it was shown that, although the femoral head changes were minimal, there was an extended variable range over which they persisted, namely from 3 to 38 months. This same variability is demonstrated in the *present study* with the average time for persistence of the x-ray change, about 12 months. However, despite the length of time involved in the healing process, there is uniform experience that the femoral head returns to almost normal structural configuration. Thus, the prognosis for this form of Legg-Calve-Perthes disease is predictably excellent.



FIG. 3. This patient presents bilateral minimal lesions in the femoral capital epiphyses. The ultimate restitution without significant deformity is the essential ingredient of these lesions.

Practically all the patients in the present report were treated with a program of abduction brace support and bed rest adhering to the principles followed in the therapy of the classical form of Legg-Calve-Perthes disease. One youngster's family declined treatment and an opportunity was thus given for long-term observation of the natural course of the disease (Fig. 6). The experience thus far accumulated suggests that the treatment time may be cut down considerably below that required in the ordinary form of Legg-Calve-Perthes disease and also that the form of therapy may be less disciplined. Preliminary probes have been made in this new direction in selected recent cases which will require future analysis.

There are two references in the literature which seem pertinent to this discussion. Caffey (2) suggested a similar pathological and clinical entity



FIG. 4. In this patient there is bilateral involvement. Both hips healed without deformity despite deep craters of both femoral articular surfaces.

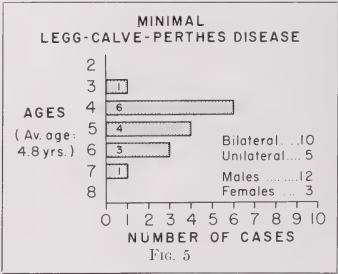




FIG. 6. This youngster came to attention because of pain and limp. Treatment consisted of several weeks of restriction in walking and then resumption of full activity. Serial x-rays reflect the stages of resolution without significant protective restriction.



FIG. 7. This 4 year old female patient exhibits eccentric surface flattening in the anterior half of the right femoral head. Final reconstitution showed tiniest indentation in films 3 years later.

with his example of "segmental ischemic necrosis of the femoral ossification center without true flattening." He further stated that "it is possible that necroses at these sites resulted from obstruction to the flow of blood through the arteries in the ligamentarteres." Mose (6) found "a predominance of young patients among bilateral cases ..." and also that "these very young cases ... often take a very mild radiological course of the disease without any greater destruction in the epiphysis."

In seven of the patients, x-rays of the carpal centers are available for analysis of bone age to judge skeletal maturity. Three patients are "average" (50th percentile); 3 patients are "slow" (10th percentile); 1 patient is "advanced" (90th percentile—Fig. 7). This small sample is unquestionably inadequate for statistical purposes and additional study is planned on the entire larger series.

Discussion

The diagnosis of Legg-Calve-Perthes disease is obvious when the clinical findings are reinforced with classical x-ray changes. Such a clear cut situation is not always available. When there is disparity between the clinical circumstances of lower extremity pain, limp and hip joint restriction and radiograph failure to show any osseous involvement, a temporizing diagnosis often has to be made. The form this has taken is exemplified by such terms as "observation hip" (3), toxic synovitis, and transient synovitis (1). Wiles found that in children with hip symptoms, 4 out of 5 proved to be of transient nature (7). Adams noted that transient synovitis "might indicate any one of a number of different conditions" (1). In my opinion, in a patient with nonspecific synovitis symptoms, Legg-Calve-Perthes disease cannot be entirely excluded until at least six months have elapsed with negative x-rays at that time. Any shorter follow-up without additional x-ray studies, may permit the diagnosis of Legg-Calve-Perthes disease to be missed and to add avoidable confusion to the recently described picture of the "late consequences of the transient hip syndrome" (3).

It has been suggested that because the symptoms of synovitis exist in both the transient hip syndrome and in Legg-Calve-Perthes disease, that the two conditions have a common origin (4). This is conjectural but an interesting concept. Perhaps the syndrome of minimal Legg-Calve-Perthes disease described in this paper is the bridge between transient synovitis and the classical Legg-Calve-Perthes disease, each representing a different grade of severity.

Conclusions and Results

1. Minimal Legg-Calve-Perthes disease appears to be an entity characterized by symptoms of synovitis and mild roentgenographic femoral head surface alterations.

2. There is a higher incidence of bilateral involvement (662/3%) than occurs in classical Legg-Calve-Perthes disease (less than 15%).

3. The average age in minimal Legg-Calve-Perthes disease is 4.8 years which is lower than the 5 to 6 year age group found in large series of Legg-Calve-Perthes disease of all severities.

4. The prognosis for femoral head reconstitution is uniformly excellent.

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Intestinal Obstruction Caused By Extrinsic Benign Myomata

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Tumors of the small intestines are relatively uncommon. Myomata (smooth muscle) tumors occur infrequently, but comprise about 40% of all small intestinal tumors. Fifty-five per cent of these are benign myomata; the remaining 45% have sarcomatous elements. There are now about 750 documented cases in the literature of all tumors of the small intestines. These tumors are located most frequently in the jejunum, 34%; 30% in the ileum and 26% in the duodenum. There is no sex differential in these tumors, which appear most frequently in people from 50 to 60 years of age. The etiology of small intestine myomata has not been determined. Experimental production of these tumors has not shed any light on the etiology, nor has any reason been determined why some tumors are subserosal and others submucosal.

In one series of 120 cases, preoperative diagnosis was made in 21% of the cases. In another series, preoperative diagnosis was made in 5% of 193 cases. It is, therefore, apparent that it is difficult to diagnose these tumors. As an aid to more frequent accurate diagnosis, the main symptoms of these tumors are reviewed. Anemia, due to blood loss, obstruction, partial and incomplete, a palpable mass and, occasionally, perforation may be present.

The diagnosis of a benign myoma of the small intestine is most difficult to make. Careful x-ray studies may reveal some abnormality. With a growing awareness of lesions of this type, and with an increasing tendency toward performing diagnostic laparotomy for continuing abdominal symptoms with negative laboratory findings, more and earlier diagnosis of these lesions will be made.

A benign tumor of the small intestines is a relatively uncommon finding. However, such a diagnosis must always be thought of in obscure gastrointestinal complaints. The excellent review of this disease by Louis River, et al (4) summarized the types of these neoplasms. The clinical study to follow has a twofold purpose: first to add two more cases to the literature, second to discuss the pitfalls of diagnosis.

Case Reports

Case #1 (TH 1203-59 E.F.)

This was the second hospital admission of a 59 year old woman who complained of crampy abdominal pain, nausea, vomiting, and constipation. The patient had been admitted six months previously for a similar episode which was relieved by a long tube, Wagensteen suction, and intravenous feedings. Her medical history included a salpingectomy in 1924, a hysterectomy and appendectomy in 1940, and removal of the cervix in 1948. There was also a history of hypertension for many years with marked EKG changes.

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Fig. 1. Tumor (opened) attached to section of resected intestine—Case #1.

On her first admission the small bowel x-ray series showed no abnormality. The diagnosis was intestinal obstruction due to adhesions.

On her second admission, the long Harris tube rapidly relieved the symptoms and, with the tube in place, a small bowel x-ray series was again done. No obstruction was found. However, physical examination revealed a small, slightly tender mass in the right lower quadrant. For this reason, the patient was explored.

The preoperative diagnosis was recurrent partial intestinal obstruction due to adhesions. The abdomen was opened through a right rectus incision. Numerous dense adhesions were lysed. In the midportion of the jejunum a tumor was found. This was extrinsic to the lumen of the gut and adherent to the other loops of the small intestine. These were freed. The loop of gut with the tumor was removed; and intestinal continuity reestablished by end-to-end anastomosis. Postoperatively, the patient did well, and was discharged asymptomatic.

The pathological diagnosis was exoenteric leiomyoma of the small intestine. (Fig. 1, 2).

Comment

The correct diagnosis had not been revealed by the x-rays. The previous operations served only to becloud the picture and prevent earlier exploration.

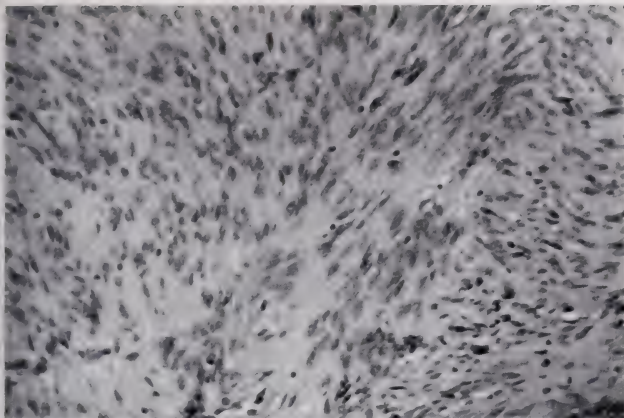


Fig. 2. Microscopic section of tumor ($\times 196$)—Case #1.

Case #2 (MSH 123878 HZ)

This was the first hospital admission of a 61 year old man transferred from another hospital. The patient had been in good health when, on vacation three days prior to admission, he began to have colicky abdominal pain. He was hospitalized with the diagnosis of gastroenteritis. However, when he began to vomit and abdominal distention became marked, he was transferred. Medical history included an appendectomy 35 years before.

On admission, there was moderate leucocytosis with a shift to the left. Temperature and pulse were within normal limits. X-rays showed low small bowel obstruction, mechanical in type. The patient was treated conservatively with a long Cantor tube, Wagensteen suction, and intravenous fluids. The tube passed into the small intestine, the intestines were decompressed, and the patient moved his bowels. A small bowel x-ray series with the tube in place was performed. (Fig. 3). This showed a sharp angulation of the small bowel in the right lower quadrant. This fixation of the loop was about $2\frac{1}{2}$ feet from the ileocecal valve. The tube was removed. Recurrence of cramps and distention made exploratory laparotomy mandatory.

There were dense adhesions throughout the abdomen. A tumor approximately the size of a grapefruit, was attached to the ileum about three feet proximal to the ileocecal valve. The tumor was adherent to all surrounding structures, was very vascular, and partially necrotic. A resection of the involved small bowel was performed with an end-to-end anastomosis. Postoperatively, the patient did well, and was discharged.

The pathological diagnosis was a large pedunculated exoenteric myoma of the small intestine showing extensive hemorrhagic infarction. There was no evidence of malignancy. (Fig. 4, 5).



FIG. 3. Small bowel x-ray with Cantor tube in lumen. Arrow points to angulation of small bowel.

Comment

Again, the previous operation, an appendectomy, served to confuse. The x-ray was not diagnostic, but did reveal that a point of fixation and angulation was present. The clinical picture was sufficient to warrant abdominal exploration.

The intestinal obstructive symptoms revealed in the two cases were in themselves nondiagnostic. However, repeated bouts of small bowel obstruction must have a definite cause which can be ascertained and corrected. The importance of exploratory laparotomy as part of a good definitive diagnostic study cannot be stressed strongly enough.



FIG. 4. Tumor showing hemorrhagic infarction attached to resected intestine—Case #2.

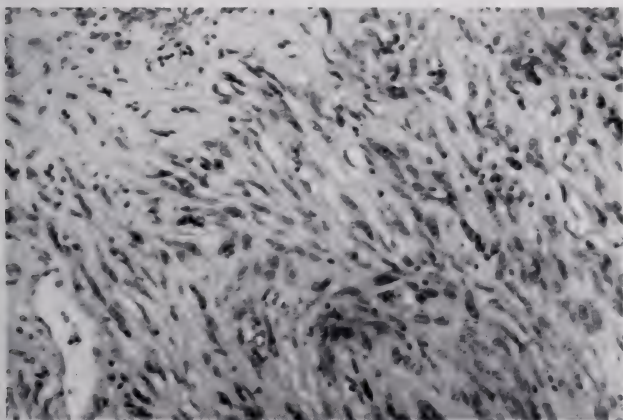


FIG. 5. Microscopic section of tumor ($\times 196$) Case #2.

Summary

Two cases of benign exoenteric myomatous tumors of the small intestine are reported. Both cases presented with signs and symptoms of intestinal obstruction. X-rays were not diagnostic in either case. Both cases had had previous abdominal surgery which helped obscure the clinical picture. Only exploration, followed by partial intestinal resection of the small bowel from which the tumor originated, and anastomosis, allowed for a complete cure.

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The Initial Contact with the Cancer Patient— Some Psychiatric Considerations

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Jacob Zaholan of Rome wrote in his seventeenth century Physician's Prayer: "...and let those not call me who are incurable and whose illness is fatal—because Thou hast decreed that they may not be cured" (1). No conscientious physician today would utter such a prayer, yet might easily sympathize with Zaholan when confronted by a patient with a life-threatening disease such as cancer.

A discussion of what to tell the cancer patient regarding his diagnosis and prognosis invariably evokes among doctors strong opinions as to whether the patient should or should not know the truth (2). Most physicians feel that the patient must never be told the facts; some feel that the patient must always be told the truth or that what the patient is told must depend on knowing the patient. So strong are the primitive responses to the threat of death, including the ultimate frustration of the physician's need to cure, that few minds are changed. We can all recognize that a poll of doctors showing that 88% believe their patients do not want to know the truth is a reflection of the doctors' own anxiety (3). Many physicians could not reveal the facts without experiencing anxiety of a degree which might well be detrimental to their dealings with the cancer patient. Yet, in their own way, doctors who never tell the truth are often able to convey to the patient a sense of security and closeness. Thus, the questions 'What to tell?' and 'Who is to tell?' must be considered concurrently. Other aspects of 'Who' include the fact that the situation for the patient under the care of a consultant or a hospital resident physician is different from that of the patient under the care of the family doctor. The family doctor in a real sense knows the patient and will treat the patient throughout the terminal illness. Although we talk of treating each case individually, it is not realistic to expect the busy physician to be able to evaluate thoroughly a patient he may hardly know, especially when both doctor and patient are under such stress. Some patients who demand absolute candor, may really be pleading for an optimistic picture. Some patients who join in a conspiracy of silence may do so in order not to offend their doctors' sensibilities. Few physicians are able to pick up enough clues on brief contact to understand these needs and make appropriate decisions. The family doctor has several choices: (1) To tell only the patient; (2) to tell only the family; (3) to tell both or (4) to tell no one. On the wards a common solution is to tell only the family. John Buchan, writing in the 1700's, discussed these matters: "It may indeed be alleged; that the doctor does not often declare

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From a Presentation to The Weekly Psychiatric Liaison Conference.

his opinion before the patient. So much the worse. A sensible patient had better hear what the doctor says, than learn it from the disconsolate looks, the watery eyes, and the broken whispers of those about him. It seldom happens, when the doctor gives an unfavorable opinion, that it can be concealed from the patient. The very embarrassment which the friends and attendants show in disguising what he has said, is generally sufficient to discover the truth" (4). Buchan does not mention the obvious disruption to the closeness the patient needs when the family cannot share such a secret with him.

A well-known surgeon passed a patient's bed on rounds and abruptly said, "Oh by the way Mrs. Jones, your report came back. It showed cancer." He then proceeded to the next bed. So unnerved were the residents that they dared to question him about this and he explained that where he had been trained it was the custom to tell the patient the truth. This was the rule he felt obliged to follow willy-nilly and so he just blurted out the news. While such instances are thankfully rare, an area that is usually given little attention relates to the question, "*How* is the news to be expressed?" Whether the doctor is warm or coldly aloof, calm or anxious, assured or guilty when revealing bad news, will affect the impact of such a revelation.

The problems confronting the doctor in his initial contacts with a patient who may die relate in part to several basic internal conflicts. The physician wants to cure and bring glad tidings, but the disease may not be curable and the tidings may be gloomy. He wants to help the patient, but instead feels like running from the situation—especially when there is a dreadful piece of news from which he feels he must shield the patient. He feels like running also because he fears involvement with someone he will lose. The patient, on the other hand, fears the worst but wants, nay *needs*, hope. What he fears more than cancer is death, and perhaps more than death he fears abandonment by those people most important to him, including his doctor. Emotional isolation of a dying patient can occur for many reasons, some obvious, some subtle. For example, when a very young woman had a breast amputation, her physicians were too upset to discuss this with her. Instead they avoided talking to her at all and tried seeing her as little as possible. When finally told that they had indeed removed a malignancy, she responded with great relief and gratitude since she had interpreted her doctors' avoidance as a most ominous sign of impending death.

We recognize that any approach to the questions we have raised must include consideration of the fact that the physician is a human being, subject to the anxieties to which his grave responsibilities expose him. We have evolved such an approach which gives the physician an opportunity to offer the truth regarding diagnosis and offer hope as well. At the same time, it also gives the patient an opportunity to deny as much as he chooses. We would prefer to allow the patient and his family to share the news and thus be drawn closer together rather than be separated by the guilt of secrecy. Our approach is quite similar to one evolved by Aldrich (5). For example, we might tell a surgical patient: "Your operation re-

vealed that you had a cancer, but the doctors are hopeful that they have completely removed it. Although one cannot offer guarantees in such a situation, we do feel optimistic about your condition." Further treatments that may be necessary such as radiation or chemotherapy can be then explained as a logical means of insuring good results and be understandable to the patient. (How often must an intelligent patient wonder, 'If the doctor says my condition was benign, why does he order radiotherapy?') With such an explanation as ours, the patient knows his diagnosis and need never suffer whispered or cryptic discussions about him or slips on the part of doctors, nurses or technicians. He can communicate openly with his family and doctor and at the same time deny as much as he needs to of the implications and possibilities of his situation. His doctor, aware of what he knows and what he needs to deny, can be open and comfortable with him and therefore less inclined to slip away since he is not troubled by the problem of keeping a secret.

We do not regard our approach as a straitjacket, but rather as a general framework. It is important to realize that this is an *initial* approach to the patient with a life-endangering illness, one which can pave the way for a more meaningful and helpful relationship between the patient and whomever is entrusted with his future care. It is an approach which makes it easier for the physician to carry out his role as a source of help and hope. The following case illustrates this technique.

A 61 year old hospitalized attorney, awaiting the report of a cervical node biopsy, asserted that if informed he had cancer he would not want to live and if told he did not have cancer he would not believe it. The house staff observed that the patient appeared depressed. Concerned about the possibility of suicide, they requested an immediate psychiatric consultation.

The patient had stated on admission that he had been well until six months prior to his hospitalization when he suffered from severe indigestion following a heavy meal. After many weeks of persistent abdominal discomfort, he reluctantly sought medical advice. Following protracted investigations, and increasing abdominal distress, he was told that he was suffering from "secondary anemia" requiring hospital treatment. The referring physician informed the house staff that the patient had a large, palpable abdominal mass, an enlarged and visible cervical lymph node, and anemia.

On admission to the Surgical Service of The Mount Sinai Hospital, the above noted findings were confirmed. Widespread malignancy was suspected. The cervical gland was removed for a tissue diagnosis, with the intention of recommending chemotherapy should the suspected diagnosis be confirmed. In the presence of proved metastases, exploratory abdominal surgery would be of no immediate value.

The patient was seen by the resident psychiatrist two days after the biopsy. Although appearing anxious and depressed, he seemed to welcome the opportunity unhurriedly to review the circumstances leading to his hospital admission. He spoke of wanting the truth, stating again that he

would not believe the doctors if he were told that everything was all right. He spontaneously went on to speak of how dependent his family had always been on him and how effectively he supported them. He recalled how his elderly mother had been placed in a mental hospital because of confusion and disorientation secondary to arteriosclerosis and given only six to twelve months to live. He took her out of the hospital, found a quiet place in the country for her to live, where with maximum tender loving care from her children she would be happy during her remaining months. She survived for ten years. He spoke of his brother's death a few years before from cancer of the kidney which had spread to the lungs. His brother, a physician, knew the diagnosis and courageously continued to work during his terminal illness. The patient admitted one additional concern: he was having pain in the lower abdomen that was becoming less amenable to the medication he was receiving.

The biopsy report came back with the diagnosis of metastatic cancer. The resident and attending psychiatrist, surgical house staff, and the social worker then formulated a plan as to what the patient was to be told about his illness and treatment. Everyone agreed that the patient must be told something in response to his own anxious questioning regarding the biopsy report. It was also agreed that the chief surgical resident was the one to tell the patient, since he would be the one to treat the patient through his terminal illness. The attending psychiatrist suggested that the patient had given many indications of his desire for the truth concerning his diagnosis, implying that like his brother, he could take the news and would successfully fight an identified foe if given some help. On the other hand, he had procrastinated in obtaining medical treatment and had stated he would not want to live if informed that he had cancer. If told of the anticipated failure of chemotherapy, and death perhaps within months, he might indeed become suicidal. Telling him that he did not have cancer and then giving him chemotherapy would in all likelihood be recognized as an outright lie and probably be regarded as equivalent to a terrifying death sentence. Such an untruth would also undermine the vitally important, developing relationship between the resident surgeon and patient.

It was decided, that the resident surgeon would tell the patient that the biopsy report revealed cancer, that he had a cancerous growth in the abdomen of a type responsive to chemotherapy and that surgery was not necessary. Chemotherapy, he would also be told, might produce discomfort but he would receive all the medication he needed for relief. Lastly, although we could not promise a cure, we were optimistic. Our hope was that this approach would allow him to recognize or deny the possibility of impending death as dictated by his current emotional needs. It would, at the same time pave the way for establishing a trusting relationship with the resident surgeon who had told him the truth, albeit a partial truth. The comment about chemotherapy causing discomfort was intended not only to prepare the patient for this eventuality but to give him the future op-

portunity to attribute to chemotherapy the anticipated abdominal pain. The social worker had seen the patient's wife briefly but had not been able to form a firm opinion about her emotional make-up. The house staff had the impression that she might not be able to tolerate the entire truth at this time. It was agreed, therefore, that the resident would talk to the patient and his wife together and would not give any additional information to the wife for the present.

The resident steeled himself for the ordeal of telling the patient, and was surprised and relieved when the patient expressed his appreciation for having been told "the truth." The patient immediately phoned some family members and told them the news, stressing the doctors' hope that he would recover with chemotherapy. That night he slept well for the first time since his admission. He subsequently told the resident psychiatrist that he was happy to hear that the doctors felt confident and that he had a "low grade malignancy" (his own words) which would respond to chemotherapy. During the balance of his hospital stay, he occasionally appeared to be anxious and on one occasion told a nurse that he was afraid of dying in great pain. Nevertheless, he continued to sleep well, was outwardly calm and in seeming good spirits, and made realistic plans for the immediate future. Just before leaving the hospital, he confided to the resident surgeon that he had known all along about the existence of the abdominal mass but that he had concealed his knowledge on admission to see what the doctors would tell him! One month following discharge, he sent a warm, moving letter of deep appreciation and admiration to the resident surgeon.

The patient's wife in contrast to her husband, realized the entire truth. She told the social worker that she recognized that her husband's condition was inoperable and that he would not live much longer. Although she never asked the doctors for further clarification, she acted upon her correct assumption. With the support of the social worker, she gave her husband nursing care, warmth, support, and encouragement in the face of progressive deterioration.

Comment

It is clear that this patient was not able either fully to accept the possibility of his early death or completely to deny the truth. Weisman and Hackett (6) suggest that for the majority of dying patients there is neither complete acceptance nor total repudiation of the imminence of death. When prompt response to treatment does not occur, and instead new symptoms arise, few patients can fully deny the obvious implications. To have told our patient the complete truth or to have indulged in a total fabrication might have prevented him from utilizing his own characteristic techniques for adapting to a painful reality and could have precipitated a severe depression.

The patient may have been voicing a fear of being placed in a position of hopelessness when he stated he would not want to live if told he had

cancer. Stehlin and Beach (7) point out that the terms hopelessness and incurability are not synonymous: "Incurability is a state of the body, whereas hopelessness is a state of mind, a giving up—a situation that must be avoided at all cost." Implied in our patient's account of the last ten years of his mother's life, was his hope for control, if not cure, of his cancer. His account of his brother's terminal illness reflected his hope that he too would be able to face this terrifying illness with courage and to continue working until death. When he voiced concern over persistent abdominal discomfort, he may well have been expressing an underlying terror of unrelieved pain and a wish for assurances of relief from such suffering.

The patient's need for open communication with, and emotional support from, both physician and family was clearly evident. Like many patients suffering from life-threatening disease, he undoubtedly felt threatened by isolation resulting from withdrawal on the part of those most important to him (6, 8, 9).

Summary

We have presented a case history of a man admitted with metastatic cancer, and have discussed the early management of a situation which is terrifying for the patient and vexing for the physician. We have used an approach which provides the patient with an appropriately timed statement regarding the nature and prognosis of his illness in terms permitting either denial or recognition of impending death, according to the patient's own emotional needs, without depriving the patient of hope. It facilitates free communication and thus allows for a closer and more comfortable relationship among the dying patient, his physician, and his family.

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The Effect of Varying Fat Diets on the Incorporation of Fatty Acids into Esters by the Small Intestine In Vitro

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Adaptation in biological systems can occur through genetic mechanisms, in which case the changes may require the passage of many generations before becoming manifest. Adaptive changes can also occur in the life span of an individual organism, presumably due to changes in enzyme composition and concentration. This latter type of change has been most extensively described in bacteria, it also occurs in higher animals, as described by Knox, Auerbach, and Lin (1). Many examples were cited, including the variations in pancreatic enzymes produced by alteration in dietary composition. In this review, there was no mention of the influence of diet on the enzymes of the gastrointestinal tract itself. Despite significant advances in our knowledge concerning the structure and function of the bowel, this area remains unclarified. Therefore, a study was undertaken to determine the effect of varying fat diets on the ability of small intestinal slices to incorporate C14 labeled fatty acid (FA) into esters in vitro. Myristic acid was chosen as the model FA, since previous work had indicated that under the experimental conditions used, this FA was incorporated into ester to the greatest extent (2).

Methods

Male golden hamsters were fed either a fat free test diet (Nutritional Biochemicals Corporation) or a regular stock diet, containing 4% fat, for the time interval indicated. The composition of the fat free diet is described in Table I. For the experiments involving a high fat diet, corn oil (Mazola) was added to the regular stock diet to raise the fat composition to 20%. Precise measurements of intake could not be made because the animals scattered their food. Each day a relative excess was offered, and they ate eagerly. Based on amount of food remaining at the end of each 24 hour period, we estimate that each animal ate 10 to 15 gm a day.

At the appropriate time interval, the test animal and the control were sacrificed. The proximal jejunum was removed, washed in saline, and everted over a glass rod. Slices (total weight 100-200 mg) were placed in 25 ml Erlenmeyer flasks containing 4 ml of incubation medium. Four to five incubations were performed on each animal.

Details of the medium composition, preparation of the FA, incubation, analysis procedure and statistical methods have been previously published (2, 3). Medium consisted of Krebs-Ringer bicarbonate buffer, half-strength

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TABLE I

Fat Free Diet	
vitamin free casein	21.10%
alphacel "cellulose"	16.45%
sucrose	58.45%
salt mixture U.S.P. XIV	4.00%
vitamin supplement as follows:	(g/100 lbs)
choline chloride	272.500
nicotine acid	27.250
inositol	13.750
vitamin A concentrate (200,000 μ /g)	4.500
vitamin D concentrate (400,000 μ /g)	3.000
alpha tocopherol	10.225
menadione	0.1025
thiamin hydrochloride	1.000
pyridoxine hydrochloride	1.000
riboflavin	1.000
calcium pantothenate	2.050

Composition of fat free diet (Nutritional Biochemicals Corporation) fed for varying periods of time.

calcium, to which had been added sodium taurocholate (Pfanstiehl), 20 μ moles/ml, and fraction V bovine albumin (Armour), 5 mg/ml. C¹⁴ labeled myristic acid (New England Nuclear), 170 m μ moles, was added to each incubation flask.

The flasks were incubated under oxygen for 30 minutes at 37° in a Dubnoff shaker. After incubation the tissue was drained, weighed, homogenized, and extracted in Dole's solution. The iso-octane phase of the Dole's solution was washed with alkaline ethanol to remove excess free FA. Aliquots were dried in planchettes, evaporated, and counted in a Geiger-Mueller counter. The per cent incorporation of myristic acid per unit weight of intestine was calculated.

All incubations were used in the calculation of the mean and standard deviation. Students' T Test was used for the calculation of the significance of the difference between the means, only simultaneous incubations being compared.

Results

Effect of a Fat Free Diet on Per cent Incorporation of FA

Three experiments were performed, comparing 6 hamsters on the fat free diet for 48 hours with 6 controls. Four incubations were performed on each animal. There was no difference in the mean weight (108 gm) of the groups at the time of sacrifice, and the hamsters tolerated the fat free diet well. No significant difference was found in the incorporation of C¹⁴ myristic acid into ester per unit weight of intestine between the two groups (Table II).

TABLE II

Effect of a Fat Free Diet on Fatty Acid Esterification by the Small Intestine In Vitro

Period on Fat Free Diet	No. of Exp.	No. of Animals in Each Group	Percent Incorporation Mean and SD		Significance
			Fat Free Diet	Control	
2 days	3	6	8.1 \pm 2.8	8.2 \pm 2.9	P > 0.5
7-8 days	5	10	4.6 \pm 2.4	5.9 \pm 2.6	0.05 > P > 0.02
1-3 months	5	6	8.0 \pm 1.5	10.8 \pm 2.8	P < 0.01

In this and subsequent experiments, four incubations were performed on each hamster. Mean, SD, and P values are derived from all incubations. Control diet contained 4% fat.

After receiving the fat free diet for 7 to 8 days, 10 hamsters were compared with 10 controls (4 incubations on each animal). The intestines of the group on the fat free diet had a lower per cent incorporation than the controls (0.05 > P > 0.02) (Table II). The group on the fat free diet had a mean weight of 106 gm. Both groups were in good condition.

Five experiments were performed on 6 hamsters after being on a fat free diet of 1 to 3 months (4 to 5 incubations on each animal). The intestine of the hamsters on the fat free diet had a lower incorporation than the controls, the difference being even more significant than after one week of diet (P < 0.01) (Table II). Although in these experiments, both groups of animals appeared in good condition, the animals on the fat free diet did not gain as much weight as the controls. Mean weight at the time of sacrifice for 4 of the animals on the fat free diet was 109 gm, while their controls had a mean weight of 140 gm.

Effect of Refeeding a High Fat Diet after a Fat Free Diet

A series of experiments were undertaken to determine how quickly the per cent incorporation would return to control values when fat was reintroduced into the diet. In 4 experiments, hamsters were placed on a fat free diet for 11 to 21 days prior to the experiment. Prior to sacrifice, the experimental and control hamsters were fasted overnight, and then fed for one hour a high fat diet containing about 45% vegetable oil. The per cent incorporation of the animals on the fat free diet remained lower than the control groups despite the one hour refeeding of fat (P < 0.01) (Table III).

TABLE III

Effect of Refeeding Fat after 2 to 3 Weeks on a Fat Free Diet on Fatty Acid Esterification by the Small Intestine In Vitro

Period of Refeeding	No. of Exp. and Animals Each Group	Percent Incorporation Mean and SD		Significance
		Fat Free Diet	Control	
1 hour	4	4.5 \pm 3.1	8.4 \pm 2.4	P < 0.01
2 hours	3	6.2 \pm 1.9	6.1 \pm 1.9	P > 0.5

Hamsters were fasted overnight, then fed a high fat diet prior to sacrifice.

In a similar manner, 3 experiments were performed in 3 hamsters on a fat free diet for 19 to 21 days, the period of refeeding with a high fat diet being extended to two hours prior to sacrifice. As before, the hamsters were fasted overnight to insure that they would be sufficiently hungry to eat the high fat diet. With a two hour refeeding period, the per cent incorporation in the experimental group was restored so that it was not significantly different from the control value ($P > 0.5$) (Table III).

Effect of a High Fat Diet on Per cent Incorporation of FA

A group of 6 hamsters were fed for 4 to 5 weeks the stock diet to which corn oil (Mazola) was added to increase the fat content to 20%. The control was maintained on the stock diet, containing 4% fat. There was no difference between the incorporation of FA in the group fed the 20% fat diet, as compared to the controls ($P > 0.5$). At time of sacrifice, the animals on the high fat diet had a mean weight of 98 gm, compared to the control value of 121 gm. Both groups appeared to be in good condition. This weight difference suggests that the hamsters disliked the high fat diet and reduced their intake. This is supported by the observation that when we attempted to study the effect of a diet containing 45% fat, the animals reduced their intake to such an extent that they lost weight, looked sick, some even dying after a period of 2 to 3 weeks.

Discussion

These studies indicate that the ingestion of a fat free diet for one or more weeks causes a decrease in the incorporation of myristic acid into esters per unit weight of hamster small intestine *in vitro*. This decrease is not reversed after the refeeding of fat for one hour prior to the experiment, but is reversed after refeeding fat for two hours. Increasing the fat content of the diet above the small amount present in the stock diet did not cause an increase in incorporation.

One explanation for our findings is that in the absence of fat in the diet, the concentration of one or more enzymes involved in FA esterification is reduced. Returning fat to the diet, induces an increase in enzyme concentration which requires about two hours to become manifest. The process is limited since further increases in fat content of the diet above the levels in the stock diet do not produce a corresponding further increase in enzyme level.

TABLE IV

Effect of a High Fat Diet on Fatty Acid Esterification by the Small Intestine In Vitro

Diet	No. of Animals	Percent Incorporation Mean \pm SD
High Fat	6	8.0 \pm 2.7
Control	6	8.6 \pm 2.9

$P > 0.5$.

High fat diet (20% fat) was fed 4-5 weeks. Control diet contained 4% fat.

Changes in enzyme composition and concentration may be induced in a variety of ways. Age, sex, seasonal and climatic changes, hormones, drugs, radiation, and substrate may all influence the enzyme composition of an organism. If the above interpretation of our results is correct, we have an example of substrate-induced adaptation, the substrate being in this case a dietary component.

Other examples of dietary-induced substrate adaptation exist. As early as 1899, the induction of lactase in the pancreas of dogs fed lactose was demonstrated (1). Lipase levels of plasma are influenced by dietary fat (1). Hexokinase levels in liver are affected by the amount of fructose or sucrose ingested (1). In 1896, Walther wrote that amylase and other pancreatic enzymes were altered by diet, the enzyme acting on the major component of the diet being secreted in the highest amount (1). This point has been controversial. Grossman et al supported Walther's findings (4). Guth et al reported variation in enzyme concentrations, but unrelated to the kinds of food ingested (5). Doubilet reported that according to his observations the enzymes of the pancreas are secreted in parallel, not affected by diet (6). Desnuelle et al measured the enzymatic activity of pancreatic homogenates, and found that amylase and chymotrypsinogen activities were related to diet (7). Trypsinogen and lipase were not affected by diet. In the intestinal tract itself, Kato observed that appropriate substrate will increase alkaline phosphatase in the duodenum of the chick (8).

It should be noted that diet can affect enzyme concentration in other ways besides substrate induction. Starvation has been noted to reduce metabolic rate more than would be expected from the reduction of body size (1). Protein depletion in starvation limits the manufacture of enzyme protein, kwashiorkor being an example of this type of enzyme deficiency. The absence of trace minerals or vitamins which serve as cofactors to enzymes may also result in a loss of enzyme function.

Kershaw et al reported that starvation decreased the capacity of the bowel to absorb glucose. This decrease may be due to protein depletion which limits enzyme production (9). Even more interesting, they reported that semistarvation significantly increases the capacity to absorb glucose *in vitro* and *in vivo*. One wonders whether this may be a type of enzyme induction of which the bowel is capable.

Other explanations for our findings, besides enzymatic adaptation, exist. A physicochemical alteration, not related to enzyme concentration, may have been produced by the fat free diet. That the physical form in which the FA is presented to the cell is important is indicated by recent findings regarding micelle formation (10). Another possibility is that an alteration in the concentration of endogenous lipid may have occurred, which in turn may influence the rate of esterification. Concentration of the endogenous lipid may have exceeded that of the model FA used. While the finding that refeeding of fat for two hours was required for the effect of a fat free diet to be reversed suggests the possibility of substrate induction, this may possibly reflect differences in gastric emptying. Even if substrate induction

is occurring, the enzymes may be responding to semistarvation, rather than the absence of fat. This possibility is not completely excluded even though at the end of 7 to 8 days there was no weight difference between the experimental and control group, while significant difference in the incorporation of FA was noted. This could only be established by the use of isocaloric diets to the control group. Also, these experiments involve an *in vitro* state which deviates from the physiological situation in that one FA predominates, to the exclusion of others. An *in vivo* state, using a mixture of FA, involving isocalorically fed controls, would add useful information.

Whether the changes in esterification noted in these experiments could be produced by an essential fatty acid deficiency, cannot be definitively answered. Since the changes described occurred within 7 to 8 days, this explanation is less likely.

Whether the changes observed with myristic acid would occur with the other long chain FA is not known. As mentioned, myristic acid was used because it is esterified to the greatest extent under the conditions studied. As chain length is either increased or decreased, incorporation decreases in stepwise fashion (2). Since there is no sudden change in behavior, but one of degree, we suspect that other long chain FA would behave in a similar fashion under the experimental conditions used. How the transport of short chain FA into the portal blood is affected by diet should also be investigated.

Summary

A study was undertaken of the effect of varying fat diets on the ability of small intestinal slices from hamster jejunum to incorporate C14 myristic acid into esters *in vitro*. Forty-eight hours on a fat free diet did not affect the per cent incorporation of FA per unit weight of intestine compared to controls on a stock diet containing 4% fat. After one week on the fat free diet, the per cent incorporation was depressed. After 1 to 3 months on the fat free diet, the depression was even more significant. Refeeding fat for one hour after a period on a fat free diet did not reverse the depression; refeeding fat for two hours resulted in a complete reversal. A 20% fat diet fed for 4 to 5 weeks did not increase the per cent incorporation above that of hamsters on the stock diet (4% fat).

While there are several explanations for the findings noted, the hypothesis is proposed that in the absence of fat in the diet, the concentration of enzyme(s) involved in FA esterification is diminished. The presence of some dietary fat may act to stimulate esterification, possibly through the mechanism of substrate-induced enzymatic adaptation.

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RADIOLOGICAL NOTES

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CASE NO. 307

SUBMITTED BY RALPH LACHMAN, M.D.

A 12 year old boy was seen at the emergency room of The Mount Sinai Hospital with painless swelling of the left side of the face of recent onset. General physical examination revealed swelling of both sides of the mandible but was otherwise negative. Radiographic studies of the mandible were obtained (Figs. 1 and 2). These studies revealed symmetrical lucent expansion



Case 307, Fig. 1. PA view of the mandible and facial bones demonstrates symmetrical lucent expansion of the body and ascending ramus of the mandible on each side (arrows). The margins are smooth, the overlying cortex is intact, and there is no infiltration of the surrounding bone. There is no tooth bud within the lucent defects.



Case 307, Fig. 2. Oblique view of the left side of the mandible again reveals a lucent defect with smooth and well-defined margins (arrows).

sion of the body and ascending ramus of the mandible on each side. The margins of the lesions were smooth and the overlying cortex intact. There was no tooth bud seen within the lucent defects to suggest follicular cysts. The roentgen features suggested the diagnosis of "cherubism." Upon further questioning, the mother described a similar problem of facial fullness throughout her childhood and adolescence.

Discussion

Familial fibrosis of the jaw (cherubism) was first described by Jones in three siblings in 1933. The roentgen appearance is quite characteristic. There is bilateral symmetrical expansion of the mandible by a multiloculated rarefaction with thinning of the overlying cortex. Characteristically the lesions begin at the angle and extend upward toward the condyles without involving them, while progressing forward to involve the rest of the mandible almost entirely. The maxilla may also show changes resulting in small or

obliterated maxillary sinuses. This latter area of involvement results in the cherubic look originally described in these patients, as the process extends to the orbital floor and infraorbital ridge.

Clinically, the onset is usually during the second year of life. Often the disease may be manifested by associated enlargement of the submandibular lymph nodes. Disturbed dentition is common. The usual pattern of the disease is for the lesions to increase in size for several years and then to remain stationary until puberty, with spontaneous regression occurring slowly over the next few decades. The lesions then are filled in with dense bone; associated remodeling may leave irregular plaques of sclerosis as the only residua.

The dysplasia apparently is the expression of a non-sex-linked dominant gene; however, the penetrance in males is 100%, while only 50% to 70% in females. Microscopic examination of biopsy specimens reveals fibrous replacement of bone in the involved areas. For this reason, it is felt by some to represent a variety of polyostotic fibrous dysplasia. The familial nature of the disease, its early onset and self-limited course, extensive bilateral symmetrical involvement and at times occurrence in the maxilla, all help to differentiate this dysplasia from other lesions of the jaw.

Case Report: FAMILIAL FIBROSIS OF THE JAW (CHERUBISM).

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CASE NO. 308

SUBMITTED BY RALPH LACHMAN, M.D.

A two week old male infant was transferred from another hospital with respiratory distress and cyanosis dating from the newborn period. Chest and skeletal roentgenograms were obtained (Fig. 1-4). Fluffy densities were present in both lungs suggesting incomplete aeration. A generalized skeletal disease was diagnosed and classified as Asphyxiating Thoracic Dystrophy.

Clinically, the infant remained critically ill and died in marked respiratory distress at the age of three months. No postmortem examination was obtained.



Case 308, Fig. 1. Supine view of the thorax includes the clavicles and humeri. The thorax is narrow, ribs short and horizontal with stubby flared ends extending only to the midaxillary lines. Clavicles are horizontal with high takeoff. The lungs are hazy bilaterally suggesting incomplete aeration.

Discussion

This disorder was first described by Jeune in 1954 (1). He reported the anomalous thoracic development in a girl who died of suffocation and whose brother succumbed in a similar manner later that year. Since that time, the syndrome must be kept in mind as a rare cause of neonatal respiratory distress. There are about twenty-one cases reported in the literature to date.

The disease is not confined to the thorax but appears to represent a generalized dystrophy. As reports of survivals appear, a tendency has occurred to refer to the entity as Infantile Thoracic Dystrophy rather than Asphyxiating Thoracic Dystrophy. That the syndrome represents a variant



Case 308, Fig. 2. Lateral view of the chest and spine shows the marked shortening of the ribs and the flaring of the anterior ends (arrow). There are six sternal ossification centers, more than the usual number present at this age. Spinal development is normal.



Case 308, Fig. 3. Anteroposterior view of the pelvis, hips, femora, and knees reveals the presence of only the distal femoral epiphysis. The pelvis is flared, achondroplastic in configuration, with small, narrow, sacrosciatic notches. Irregularities are noted at the distal femoral metaphyses.

of Chondroectodermal Dysplasia (Ellis-Van Creveld) has been discarded by most authors, although some similarities are striking.

The chest x-ray usually suggests the diagnosis. Figures 1 and 2 show the classical findings. The thorax is narrow and elongated. The clavicles are horizontal and high in position. The ribs are short and horizontal and appear to end laterally at the midaxillary lines with clubbing of their anterior ends. An increased number of sternal ossification centers in the newborn period has recently been described which was also noted in this case (Fig. 2). Fluffy pulmonary infiltrates are often present.

The pelvis is achondroplastic in configuration with flaring and squaring of the iliac wings. Narrow sacrosciatic notches are present (Fig. 3). Metaphyseal splaying and irregularities have been described, suggesting an abnormality at or near the zone of provisional calcification (Fig. 3 and 4). Some shortening of ulna and fibula may also be associated, not apparent in



Case 308, Fig. 4. Anteroposterior view of the left hand and wrist reveals a radiolucent line at the distal ulnar metaphysis and a suggestion of a similar line at the distal radial metaphysis; these presumably represent abnormal zones of provisional calcification. No carpal centers are present. An unusually long and thin distal phalanx is seen in the thumb.

this patient. Microscopic examination in one case revealed this zone to be very limited in size and associated with decreased vessel penetration. The knobby anterior ribs were caused by hyperplastic cartilage.

Several cases with survival beyond the critical newborn period have been followed to preadolescence, at which time there is a tendency towards a reversal to normal with few residual abnormalities. It is noteworthy that this patient has at least one normal sibling, since a definite familial tendency has been established. The trait is considered to be transmitted by an autosomal recessive gene.

Case Report: ASPHYXIATING THORACIC DYSTROPHY

Acknowledgment

This case is presented through the courtesy of William Bernstein, M.D. Good Samaritan Hospital, Suffern, N.Y.

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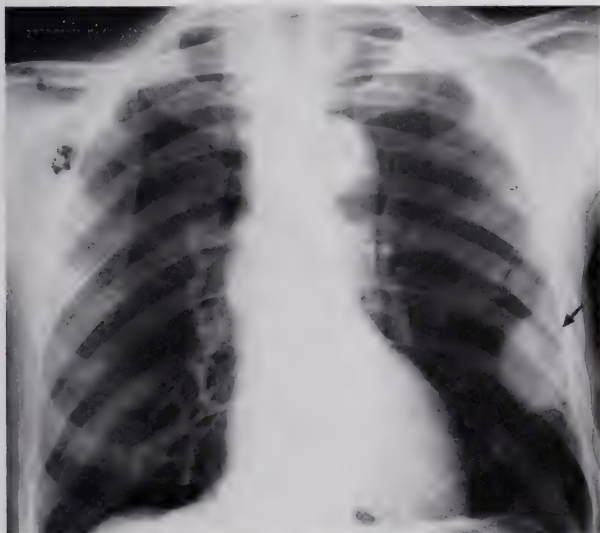
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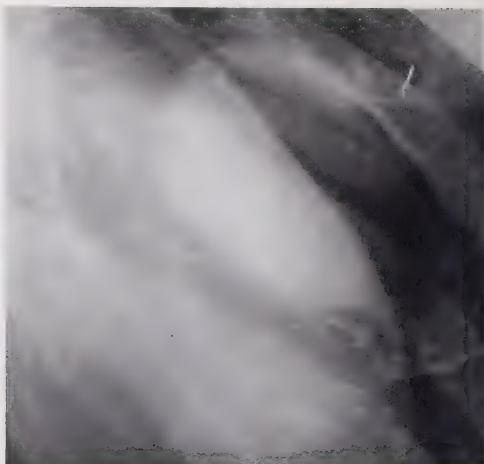
CASE NO. 309

SUBMITTED BY SAMUEL ANDELMAN, M.D.

An 83 year old man was referred for a routine chest x-ray. A soft tissue mass was noted overlying the left 7th, 8th, and 9th ribs posterolaterally measuring 5 cm in diameter (Fig. 1 and 2). The medial margin of the lesion was smooth, sharp, and regular, while the lateral margin was not demarcated from the chest wall. A slight concave indentation with marginal sclerosis was noted along the inferior border of the 7th rib adjacent to the lesion. A benign, slow-growing extrapleural neoplasm was diagnosed. Needle biopsy was performed. The histologic diagnosis was neurofibroma.



Case 309, Fig. 1. Posteroanterior roentgenogram of the chest reveals a 5 cm ovoid soft tissue mass related to the left 7th to 9th ribs posterolaterally. The medial margin is smooth, sharp, and regular, while the lateral margin is not demarcated from the chest wall. Arrow points to a slight concave indentation with marginal sclerosis along the inferior border of the 7th rib.



Case 309, Fig. 2. Magnified view in right anterior oblique projection emphasizes the well-defined medial margin, absent lateral margin, and the effect on the 7th rib (arrow).

Discussion

See Discussion following Case No. 310.

Case Report: EXTRAPLEURAL NEUROFIBROMA.

Acknowledgment

This case is presented through the courtesy of Paul Kirschner, M.D.

CASE NO. 310

SUBMITTED BY SAMUEL ANDELMAN, M.D.

A 48 year old man was referred for a routine chest x-ray. A soft tissue mass was noted overlying the right 7th and 8th ribs posterolaterally measuring 4.5 cm in diameter (Fig. 1 and 2). Although the medial margin was somewhat ill-defined in the frontal projection, it was smooth and sharply defined in the right anterior oblique projection. The lateral margin was not demarcated from the chest wall. A minimal scalloped defect was noted along the inferior margin of the adjacent 7th rib. The lower extent of the lesion made an obtuse angle as it merged with the shadow of the chest wall. A benign, slow-growing extrapleural neoplasm was diagnosed. Surgical biopsy was performed. The histologic diagnosis was lipoma.

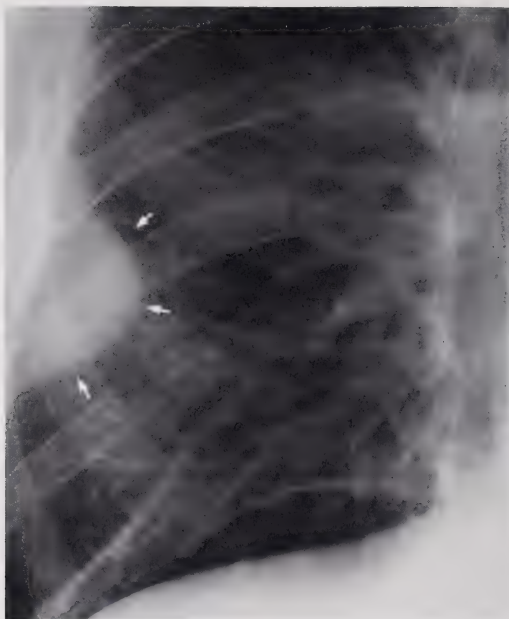


Case 310, Fig. 1. Posteroanterior roentgenogram of the chest reveals a 4.5 cm mass overlying the right 7th and 8th ribs posterolaterally. The medial margin is somewhat ill-defined (medial and inferior arrows). The lateral margin is not demarcated from the chest wall. A minimal scalloped defect is noted along the inferior margin of the adjacent 7th rib (superolateral arrow).

Discussion

Cases 309 and 310 are presented as typical examples of benign extrapleural tumors. Anatomically, the extrapleural space is a potential space bordered by ribs and parietal pleura, and containing nerves, blood vessels, muscle, and areolar tissue. Any element may give rise to neoplasm, but neurofibroma and lipoma are the most frequent benign tumors, while metastatic carcinoma to rib is the most common malignant tumor.

The roentgen features of extrapleural tumors are illustrated by both the cases presented. The surface of the mass covered by pleura is sharply outlined as it projects into the surrounding lung, while the peripheral margin of the lesion is not demarcated from the soft tissues of the chest wall. An obtuse angle may be formed as the margin of the mass merges with the chest wall as in Case No. 310; an acute angle would imply a pleural origin. Appropriate oblique view may be necessary to provide the optimal tangential



Case 310, Fig. 2. Magnified view in right anterior oblique projection reveals a smooth, regular, sharply defined medial margin (arrows). The lower extent of the lesion makes an obtuse angle as it merges with the shadow of the chest wall.

projection to demonstrate this feature. Finally, a slowly growing mass may produce an erosive bony defect, as in both cases presented. A sharp scalloped defect, often with sclerotic margin of condensed bone, is thus contrasted with the infiltrative lesion associated with a malignant process.

Neurofibroma may occur as an isolated tumor or as a manifestation of Von Recklinghausen's disease. In the thorax, it may arise from an intercostal nerve usually in relation to the intervertebral foramen and paravertebral gutter. The more peripheral location, as in Case No. 309 is less common.

Extrapleural lipoma is a relatively rare tumor. An interesting diagnostic sign is compression of the tumor by the expanding lung in deep inspiration.

Case report: EXTRAPLEURAL LIPOMA.

Acknowledgment

This case is presented through the courtesy of Paul Kirschner, M.D.

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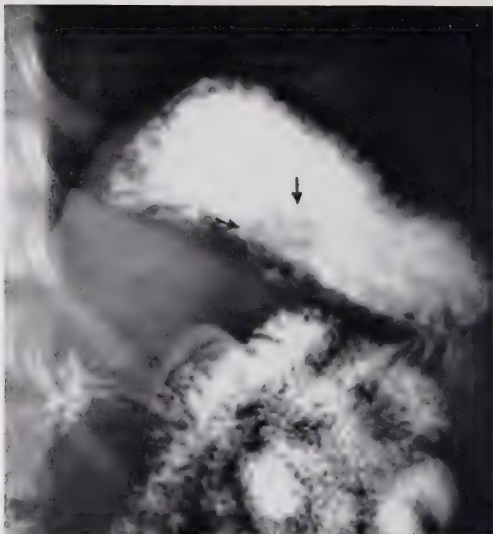
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CASE NO. 311

A 35 year old woman was referred for gastrointestinal series because of vague discomfort in the epigastrium and left upper quadrant. Past history and general physical examination were noncontributory.



Case 311, Fig. 1. Right anterior oblique erect view of the stomach from gastrointestinal series reveals a 2.5 cm lucent defect in the barium column in the upper portion of the body of the stomach. The superior margin is quite sharp (arrows). The lateral and inferior margins fade away. No other abnormality is noted.



Case 311, Fig. 2. Left posterior oblique view with small amount of barium delineates a normal mucosal pattern. Arrow again points to the sharp superior margin of the lucent defect. No ulceration is present.

The films revealed a 2.5 cm round defect in the upper portion of the body of the stomach (Fig. 1 and 2). The superior margin of the defect was quite sharp, while the inferior and lateral margins faded away without demarcation. No ulceration or other abnormality was noted. The study was repeated some weeks later and the shadow persisted unchanged. The diagnosis of an intramural or submucosal tumor, such as a myoma, was advanced.

The patient was explored. The stomach was opened and carefully inspected and palpated. No lesions were found. However, in the retrogastric area, a small round mass was noted in relation to the vessels near the hilum of the spleen. There was no unusual adhesion or fixation present. Splenectomy was performed with the mass included in the specimen. Pathologic examination revealed a discrete aneurysm of the splenic artery.

Discussion

This case illustrates the difficulty which may arise in establishing the location of a mural defect. The sharp upper margin as seen here implies

close apposition of the overlying mucosa to the edge of the mass and a mural tumor in a submucosal location should come first to mind. The fading lower and lateral margins do not go along with this, however. The implication of this latter finding is to place the tumor further from the mucosa, i.e., intramural or subserosal in location, or to suggest a lesion entirely outside the gastric wall. The sharp upper margin might be better understood if adhesions or fixation of the structures were present; these possibilities are excluded in this case by the careful surgical exploration. The features of a mucosal lesion such as altered overlying mucosa and intraluminal projection are not present.

In summary, an extrinsic lesion can indent the stomach in a discrete fashion and produce the sharp margination which usually implies an intramural submucosal location.

Harvey M. Peck

Case report: ANEURYSM OF THE SPLENIC ARTERY MIMICKING AN INTRAMURAL TUMOR OF THE STOMACH.

Acknowledgment

This case is presented courtesy of A. David Schwartz, M.D. and Lester Lando, M.D., Good Samaritan Hospital, Suffern, N. Y.

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Development and Goals of a Trauma and Shock Research Center*

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Introduction

During the Second World War the development of trauma hospitals in several European centers greatly facilitated the management of severely injured patients. The Birmingham Center in England and the German trauma hospitals are examples of this approach. In this country, large city and county hospitals are unique among civilian hospitals in that they receive most of the city's trauma patients. Private hospitals frequently are unable or unwilling to invest in the supporting facilities required for trauma centers largely because of the tremendous costs and the socioeconomic level of most of the trauma victims. By default most of the shock and trauma cases are sent to the center-city charity hospitals. In private hospitals, intensive care units have become standard means to provide coordinated emergency services from each of the relevant medical specialties as well as intensive nursing care for acutely ill patients. Many of these clinical centers have investigated problems of shock from surgical trauma, sepsis, and myocardial infarction. These conditions, although widely different from the point of view of etiology, have many aspects in common. They are acute illnesses in which the patient is in imminent danger of life-threatening shock from cardiovascular and metabolic problems.

The major purpose of a shock and trauma center, emergency room or intensive care unit is the resuscitation and management of the acutely ill patient. In the past the clinical trauma literature has emphasized evaluation of specific therapeutic regimens and the clinical management of specific types of injuries. These activities are necessary for the prevention and treatment of sudden, life-threatening emergencies which is the overriding preoccupation of this type of service.

An appropriate function of these centers is the gathering of clinical data for descriptions of the natural history of a wide spectrum of patient problems including mass casualties, auto accidents, postoperative states, acute

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myocardial infarction, sepsis, specific kinds of fractures, soft tissue wounds, nerve injuries, and the description of unique aspects of unusual cases. Descriptions of clinical syndromes are necessary to provide the basis of expeditious diagnoses and evaluations. Clinical centers also should be concerned with systematic inquiry into basic mechanisms involved in acute injury. Ultimately, solutions of the peculiar problems encountered in acute illnesses must be sought through application of the methods and approaches of the basic medical sciences.

Evaluation of the Disturbed Circulation

Blood pressure, pulse rate, temperature, and respiratory rate, the so-called vital signs, are the conventional means of evaluating the circulatory status in acute illnesses. These signs are readily and routinely obtained by nurses at frequent intervals. In charted form, vital signs are the standard method of following the course of relatively short-term circulatory changes and to warn of impending problems. However, measurements of pressure and changes in pressure are nonspecific indices of the circulatory status. They reflect the sum of all compensatory reactions along with the primary circulatory defect or the degree of shock.

Recent advances in biomedical engineering have provided continuous recording of arterial and venous pressures, heart rate, EKG, and other information. The data can be displayed visually and recorded on media compatible with analogue and digital computers; automatic visual or auditory signals may be set off when pressures or heart rates rise above, or fall below, preset values. Automation techniques, while they may improve the accuracy of the measurement and facilitate the recording of data, do not obviate the limitations of the measurement or provide additional insight into the fundamental problems.

Several other clinical tests have found wide application to the evaluation of acute circulatory problems: (a) The hematocrit is useful to assess an initial episode of blood loss, provided there is time for transepillary migration of interstitial fluid into the plasma water. The hematocrit also has rather severe limitations for reflecting changes in blood volume during periods of blood and fluid administration; (b) The central venous pressure is a good indication of overtransfusion and, as such, it is an important endpoint; (c) Reduced urinary output may reflect either inadequate renal blood flow from reduced blood volume or impaired renal function. If there is no preexisting renal damage and if urinary specific gravity is greater than 1.018, urine output may reflect tissue perfusion of this one important organ. (d) Blood volume measurement, if properly done, is the best means to quantify the volume of blood remaining in the circulation, and indirectly the volume of blood lost.

Cournand, *et al* (1) and Richards (2) first used cardiac catheterization and the direct Fick method for measurement of cardiac output to evaluate the circulation of shock patients at Bellevue Hospital. They observed decreased cardiac output and increased peripheral resistance in shock patients who had sustained hemorrhage. They also observed similar findings in trauma patients

who had sustained multiple fractures (1, 2). In the minds of many, shock has come to mean the acute circulatory failure associated with low cardiac output and high resistance. Subsequently, others investigated the hemodynamic alterations of septic shock in man (3-5). More recently, several groups of workers have reported measurements of cardiac output in rather small numbers of patients with various etiologic types of shock (6-11). Unfortunately, somewhat disparate findings have been reported; low cardiac output with high resistance, normal output with normal resistance and high output with low resistance have been described. The variety of responses, with differences in methods, and the small number of subjects, make it difficult to separate methodologic and technical problems from the actual development of hemodynamic changes in shock of different and frequently unknown etiologies. This underscores the need for a systematic study of hemodynamic changes over the entire time course of development and recovery from shock; such a study which must be carried out in large numbers of subjects, with different but well-defined etiologies.

Simultaneous measurement of cardiac output together with heart rate, systemic arterial pressure, and right atrial or central venous pressures permit derivation of a number of pressure-flow relationships which may be used to approach various physiologic factors that are not directly measurable; e.g. vasomotion, stroke volume, myocardial oxygen consumption, ventricular contractility, and cardiac work. When pulmonary arterial and left atrial pressures are obtained, the derived values (e.g., pulmonary vascular resistance, right ventricular stroke work, right heart work) may be calculated for the pulmonary circulation in a similar manner to that of the greater circulation. In addition to their importance as reflections of the circulatory state, these hemodynamic measurements also are important because they provide information upon which metabolic reactions may be quantified and correlated.

This approach can provide information relevant to important unanswered questions. Some of these specific questions are:

1. Which of the hemodynamic responses in each of the various etiologic types and stages of the shock syndrome are compensatory and have survival value?
2. When and how do these compensatory hemodynamic reactions decompensate and contribute to death?
3. When and to what extent is noncardiogenic shock due to central pump failure?
4. When and to what extent is cardiac insufficiency (as opposed to overt cardiac failure) a limiting factor in noncardiogenic shock?
5. What are the external influences, associated clinical conditions, and intrinsic homeostatic influences which affect cardiac output?
6. What is the relation of vasoconstriction to the development of acute circulatory collapse?
7. When and how does peripheral vascular failure lead to the stage where the patient is no longer responsive to further blood transfusions?
8. What is the role of microcirculatory alterations in the development of peripheral vascular failure?

9. What is the relation of increased pulmonary vascular resistance to postshock pulmonary complications?
10. What are the relationships of cardiac output and arterial and mixed venous O_2 and CO_2 tensions to O_2 and CO_2 transport?
11. What are the interactions among changes in ventilatory and respiratory function, cardiac output, red cell mass, and O_2 transport during the development of the shock state?
12. What are the relationships of hemodynamic events to the metabolic derangements?
13. What is the relation of changes in the body's O_2 consumption and the available supply of oxidative substrates under normal and shock conditions?
14. What are the interactions between the availability of oxygen to individual organs and their metabolic requirements in the normal and disturbed circulations?
15. What are factors which control the capacity of the liver to clear organic acids and supply glucose under normal and stress conditions?

In the past few years we have accumulated some data in an effort to provide partial answers to a few of these questions. The data from our first hundred study patients were separated according to etiologic categories: hemorrhage, trauma, sepsis, and various combinations of these. The results, summarized in Figures 1 and 2 show that the information obtained by this approach was not particularly useful; about the only conclusion that could be drawn was that shock is associated with hypotension, tachycardia, and somewhat inconsistent changes in cardiac output, mean transit time, peripheral resistance, and other derived calculations.

It was apparent from perusal of the data from individual patients that a major neglected aspect in the evaluation of the acutely disturbed circulation was the failure to recognize differences in the time sequence of the hemodynamic alterations. Then we (12-14) analyzed these data and that of subsequent patients according to more precise etiologic criteria, degree of hypotension, time sequence, other clinical manifestations, and final outcome. We described a sequence of hemodynamic events in patients with hemorrhage unassociated with trauma or sepsis (13, 14) and in patients who had trauma with and without anesthesia (12). The pattern of events was initially assessed by arbitrarily separating sequential events into stages according to changes in arterial pressure and other clinical criteria. Then the patterns of hemodynamic events in the disturbed circulatory state arising from hemorrhage were compared with, and differentiated from, those following trauma, burns, sepsis, anesthesia, and cardiogenic factors as well as the various combinations of these.

Hemodynamic Response to Hemorrhage

Serial cardiovascular measurements were performed in 12 patients who had sustained hemorrhagic shock without significant tissue trauma or sepsis (13,

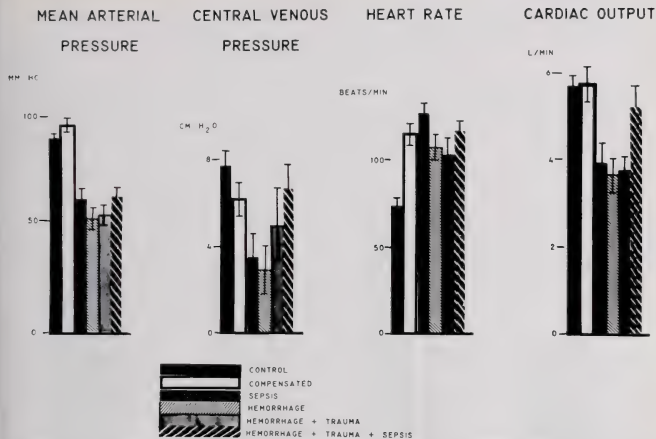


Fig. 1. Hemodynamic measurements observed in a series of patients with various etiological types of shock. The values represent initial observations which were made when the patient first was observed by the service. Bars represent mean values, lines at the top of the bars represent S.E. of mean. The first solid bar represents 17 control subjects. "Compensated shock" was considered to be present when the patient had been in shock but the arterial pressure was restored by the time of the initial measurement.

14). The observations were begun shortly after the patient's admission to the hospital and continued until the patient recovered from his circulatory problem or died. Nine of twelve patients with sudden acute hemorrhage in this series had an initial hemodynamic response consisting of reduced cardiac output and normal or high peripheral resistance (Fig. 3); this was consistent with the previous findings of Cournand *et al* (1) and Richards (2). There were also suggestive decreases in arterial pressure, central blood volume, stroke index, and stroke work as well as increases in heart rate and mean transit times. There was a prompt return to near normal values after volume replacement in this group.

High cardiac output and normal or low resistance were observed in two patients who had high blood alcohol levels and in one patient who also sustained head injury with cerebral concussion. After blood volume replacement this group also had further increases in cardiac output. These data suggest that the cardiovascular set was altered by alcohol or direct head injury, possibly through their action on central vasomotor centers.

Four hemorrhagic shock patients were studied in a preterminal state; they had hypotension with relatively normal cardiac output and resistance measurements (Fig. 4). In this group, there was suggestive evidence of reduced stroke index and stroke work index, as well as increased mean transit times

HEMODYNAMICS IN CLINICAL SHOCK

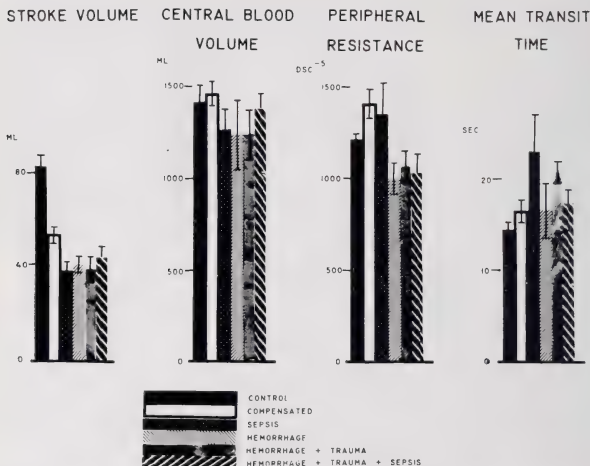


FIG. 2. Hemodynamic measurement in a series of patients with various etiologic types of shock (continued). Designations as in Figure 1.

and heart rate. In the terminal stage, cardiac output fell precipitously, venous pressures rose abruptly, and arterial pressures continued to fall. The latter observations are consistent with the hypothesis that the final events result from myocardial insufficiency and failure of compensatory peripheral vascular mechanisms which may be maximally operative in the antecedent stages (13-15).

Hemodynamic Response of Anesthetized and Unanesthetized Patients after Trauma

The sequence of hemodynamic events after acute trauma was observed by serial hemodynamic measurements in 41 patients who had sustained unanesthetized trauma including gun shot wounds, blunt abdominal trauma, fractures, burn trauma, and stab wounds, and in twelve patients who were studied before, during and at various periods after operative (*i.e.* anesthetized) trauma (12). After trauma there was increased cardiac output, decreased peripheral resistance, and increased heart rate. In some cases increased central venous pressure, decreased stroke volume, and increased transit times were observed. The increased cardiac output persisted to the pre-

HEMODYNAMIC CHANGES IN VARIOUS STAGES OF SHOCK

PERIOD OF HEMORRHAGIC SHOCK

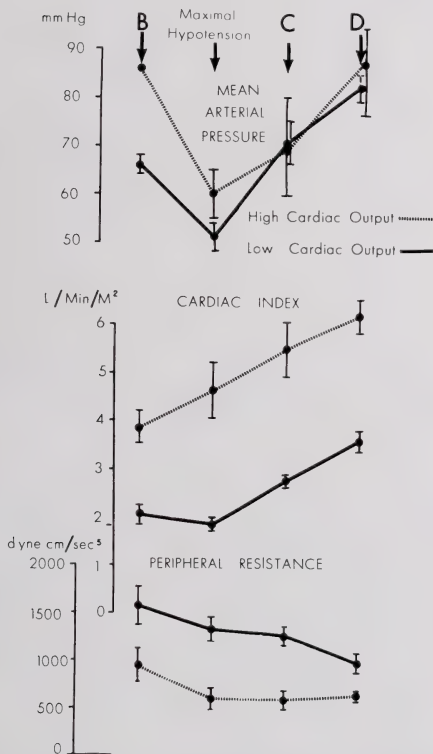


FIG. 3. Sequence of changes in arterial pressure, cardiac index, and peripheral resistance in a series of patients who sustained acute blood loss. The solid line represents the mean values and S.E. of the mean of 9 patients with uncomplicated hemorrhage (low cardiac output group). The dotted line represents the values in 3 patients whose hemorrhage was complicated with inebriety or head injury. Period B was defined as the early period immediately after blood loss when arterial pressures were falling. This period was arbitrarily separated from period C, the middle period, by the point of maximal hypotension. Period D, the late period, was defined as the period after apparent recovery from the point of view of vital signs.

CARDIOVASCULAR EVENTS AFTER PROLONGED HEMORRHAGE PRETERMINAL & TERMINAL STAGES

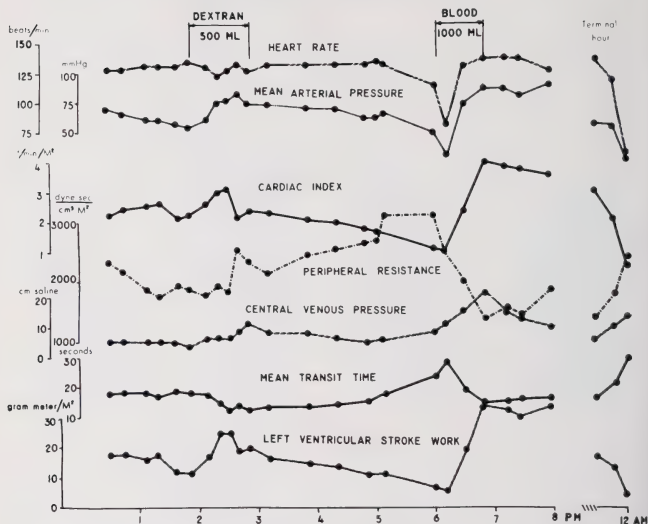


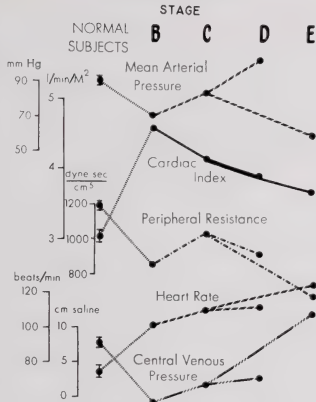
FIG. 4. Data from a patient who had received 8 pints of blood during an upper gastrointestinal hemorrhage. The patient was monitored over an 8½ hour period and, following a 2½ hour interval, during the terminal hour. Measured blood volume taken at the onset of the study showed a deficit of 1180 ml. During dextran administration cardiac output and arterial pressures were restored temporarily to relatively normal values, the mean transit times and central venous pressures decreased, the left ventricular stroke work was somewhat improved, and blood volume was partially restored. Prior to the blood transfusion at 6 PM, the blood volume was 880 ml deficient and after transfusion of 1000 ml of whole blood it was only 380 ml less than the calculated normal. At this time cardiac index increased to over 4 L/min/M² and resistance decreased below normal levels. There was also partial restoration of arterial pressure, stroke work, and mean transit time. In the terminal period cardiac output, arterial pressure, heart rate, and stroke work fell precipitously; resistance, venous pressure, and transit time rose. From Monson and Shoemaker (12) with permission of authors and publishers.

terminal stages where hypotension, rapid pulse, and elevated venous pressure occurred (Figs. 5, 6).

In general, the increased cardiac output was greater with more severe and extensive trauma. The increase occurred early; it was frequently present during periods of hypotension which were unassociated with blood loss; it persisted beyond the period where vital signs had returned to preoperative levels. In fatal cases the increased cardiac output persisted to the preterminal stage (12). In the final moments of life the cardiac output frequently declined

EFFECTS OF UNANESTHETIZED TRAUMA ON HEMODYNAMICS

FIG. 5. The effects of trauma in a series of 22 unanesthetized patients who had sustained gun shot wounds. The average values for mean arterial pressure, cardiac index, peripheral resistance, heart rate, and central venous pressure in a series of 17 normal subjects is shown on the left column. Values for the series of patients with gun shot wounds are shown during four time periods: "B" early, "C" middle, "D" late stage for patients who recover, and "E" late or pre-terminal stage for patients who go on to die. There is an early increase in cardiac output, a progressive fall in resistance and a progressive rise in heart rate and central venous pressures after this type of unanesthetized trauma. From Shoemaker et al (12) with permission of the publisher.



abruptly. The final agonal event is characterized by reduced cardiac output, peripheral resistance, and arterial pressure as well as increased heart rate and venous pressure.

Hemodynamic Response to Sepsis

Fifteen patients were studied while they were in a state of shock in which sepsis was the primary, if not sole, etiologic factor of their illness. Nine of these patients were young, otherwise healthy females who had septic abortions. The trauma involved in the instrumentation, which induced abortion, preceded the hospital admission by 3 to 5 days and was considered minimal in each case; none of these patients who were studied lost more than 300 ml of blood. In the six other septic patients, shock was attributable to peritonitis from perforated appendicitis (2 patients), from perforated peptic ulcer and from diverticulitis of the colon, acute pyelonephritis, and pancreatitis. Effort was made to obtain measurements as early as possible in the course of the septic process. When first seen by the Trauma Service, the initial measurements of cardiac output were increased in 6 patients, decreased in 7 patients and within normal limits in 2 patients. The average cardiac index of the series was 3.67 ± 0.57 (S.E.) l/M²/min.

The patients were separated by arbitrary criteria into early, middle, and late periods by dividing the total period of sepsis from onset of fever to demise into roughly equal intervals. The time sequence of septic shock syndrome was less clearly defined than that following hemorrhage and trauma. In part,

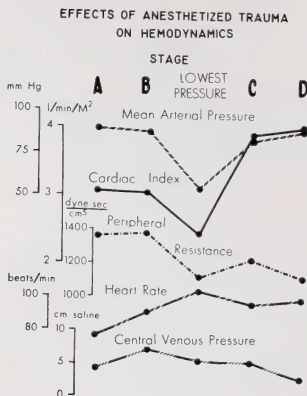


FIG. 6. Effects of trauma on hemodynamics in a series of 12 patients studied before, during and after extensive surgery. Designation for hemodynamic values as in Figure 5. Stage "A" is the pre-operative control period. Stage "B" and the period of lowest arterial pressure most frequently occurred during the operative period, but occasionally these stages were observed in the immediate post-operative period. Stage "C," the middle period usually was seen in the first 12 to 24 hours postoperatively during which time the patient had evidence of some circulatory instability. Stage "D" was after the patient had recovered from the point of view of vital signs. There was a decreased cardiac index during the period of hypotension, but an increase thereafter. Resistance fell progressively, while minor elevations in heart rate occurred. From Shoemaker et al (12) with permission of the publisher.

this may have been due to the difficulties of determining the exact onset of the syndrome as well as to the more protracted course of the septic shock syndrome. The average cardiac index observed in the early stage was 2.8 l/M² min, in the middle stage it was 6.2 l/M²/min, and in the late stage it was 2.7 l/M² min. In general, the cardiac output decreased with dehydration and fluid loss, but increased with high body temperatures.

The Pattern of Changes of Cardiac Output in Various Types of Shock

Initial description of the shock state in terms of variations in cardiac output and other hemodynamic events suggested that variegated shock syndromes may be appropriately redescribed in terms of the underlying hemodynamic, physiologic and metabolic aspects. Ultimately, such a hemodynamic and physiologic description may provide a sounder and more rational basis for therapy. That is, precise indications and contraindications of each agent may be based upon the physiologic defects found to be present. Moreover, new therapeutic agents may be sought to counter the specific physiologic abnormalities observed.

Figure 7 is a schematic representation of our initial working hypothesis, for the pattern of development of the shock syndrome arising from hemorrhage, trauma, burn, and sepsis. It may be seen from this figure that patterns of the disturbed circulations resulting from various etiologies have some similarities. However, differences in the duration of hemodynamic alteration of each etiologic type are striking. Hemodynamic events after hemorrhage may be measured in hours; the pattern after trauma occurs in a period of 2 to 5 days

CARDIAC INDEX PATTERNS IN VARIOUS TYPES OF SHOCK

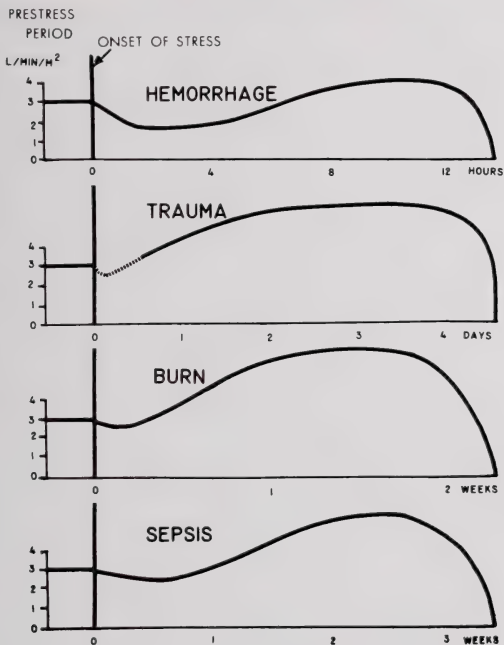


FIG. 7. Schematic representation of the time sequence of cardiac index changes in shock induced by various events from the onset of the shock-inducing agent to the time of death.

and changes after burns and sepsis may persist for a week or more. This time disparity may be attributable in part to the length of time that the etiologic agent influences the body's responses as well as the nature and form of the etiologic event. Hemorrhage is often rather sudden, the damage from trauma, incident to either surgical procedures or accidents may persist for several days, and the deleterious influence of major burn or septic process may last for days or weeks. The hemodynamic effects of the particular stress probably last as long or longer than the duration of the stress itself. Thus, not only the nature but also the duration of the etiologic event may determine the character of the ensuing shock state.

When the variability of the time course of the shock state is taken into

TABLE I
Factors Influencing Cardiac Output

Increase	Decrease
<i>A. Related Clinical Conditions</i>	
Anxiety Muscular activity, exercise Anemia Hypoxemia Intracranial injury Hyperthermia Hypercarbia Acidosis Catabolic end-products; lactic acid, polypeptides Ventilatory failure, partial airway obstruction Pneumonia and other pulmonary disease Hypermetabolic states; e.g., hyperthyroidism Arterial-venous shunts Arterial-venous fistula in major vessels	Hypovolemia Dehydration Hypothermia Arrhythmias Alkalosis Hypocarbica
<i>B. Drugs</i>	
Anesthetic agents; e.g., cyclopropane Alcohol Isoproterenol Norepinephrine Metaraminol	Anesthetic agents, e.g. pentothal Morphine, other anodynes especially in the presence of pain and anxiety Methoxamine (on occasion)

consideration, the similarities among the various etiologic types of shock are striking. In hemorrhage, it may be seen that there is an initial decrease in cardiac output which gradually returns toward normal in those patients who recover. In those patients who die, cardiac output often remains normal or high up to the preterminal state, but may fall abruptly during the final agonal event (Fig. 4). In trauma and sepsis the initial fall in cardiac output may be transient, attenuated or absent. But unless careful observations are obtained early in the course of the disease, the early hemodynamic responses will be missed. These general patterns are influenced by many factors, some of which are listed in Table I.

These observations on noncardiogenic shock may be related to previously reported series (10, 11) which have demonstrated low cardiac output after myocardial infarction.

Significance of Increased Cardiac Output

The significance of increased cardiac output after trauma at present is obscure, but it is possible that certain specific mechanisms may be implicated (Table I). Pain, anxiety, and other emotional states accompanying severe

trauma produce increased cardiac output. Although these factors undoubtedly play a role in many cases, we have observed the increased output when little or no anxiety was manifest, when patients were resting quietly, and when patients were semiconscious or comatose.

It is possible that overtransfusion may increase cardiac output; as blood volume loss may produce decreased cardiac output; it is theoretically possible that increased blood volume may increase blood flow. Against this hypothesis was the observation that normal blood volumes were found in the majority of the patients with high cardiac output. Moreover, transfusion therapy in normovolemic shock patients of these and previous studies (15) did not appreciably increase cardiac output.

The influence of alcohol was a factor in the unanesthetized trauma patients. Blood alcohol concentrations were measured routinely in patients where inebriety was evident or suspected; they were elevated in six patients. In the immediate period after injury, alcohol may have contributed to the increased cardiac output. However, it was not thought likely that alcohol ingested before injury would continue to stimulate cardiac output for periods of 2 to 5 days.

Neural and hormonal influences which stimulate cardiac output are initiated at the time of injury and may continue to be operative, since they are stimulated by the injured tissues. These influences may not be dependent entirely upon appreciation of pain since increased cardiac output was observed when patients were under surgical anesthesia. Increased adrenal output of epinephrine and norepinephrine, with resultant increased circulating levels of catecholamines, may stimulate the heart by their inotropic action. Compensatory increase in cardiac output also may be stimulated because of increased oxygen need from many mechanisms. For example, epinephrine is known to increase tissue oxygen utilization by uncoupling oxidative phosphorylation; this reaction, which increases the rate of tissue oxygen uptake, may require increased tissue perfusion.

Increased cardiac output may compensate for a relative failure of oxygen transport. Anemia, arterial oxygen desaturation, and failure of respiratory or ventilatory function are examples of clinical conditions where high output failure may occur acutely. Fat emboli, the release of lipids from fat stores, denaturation of plasma proteins, vasoactive hormones such as serotonin, vasopressin and oxytocin have a profound effect on the circulatory dynamics. Some catabolic end-products with vasoactive properties, such as peptides, directly and indirectly, affect the circulation.

Many of the factors which influence changes in cardiac output in traumatic and hemorrhagic shock also are operative in septic shock. In addition, there are influences which are peculiar to sepsis. High fever increases body metabolism and requirements for transport of O_2 , CO_2 and breakdown products of metabolism. Increased output also may be stimulated directly by bacterial agents and their endotoxins or indirectly from bacterial action.

Increased cardiac output may be stimulated by other subtle influences. It may be that acute injury produces a more inefficient circulation which re-

quires greater blood flow rates. Alterations in regional blood flow, local or generalized hypoxia, cellular aggregation, viscosity changes and failure of perfusion at the capillary level may stimulate compensatory increase in total body perfusion which would be observed by increased cardiac output rates. Tissues locally injured or even tissues remote from the injury required greater perfusion rates because of the disturbed circulation set up by the acute injury.

Use of Hemodynamic Measurements to Evaluate Therapy

The relative effectiveness of various therapeutic regimens in each etiologic type, degree, and stage of shock may be compared by hemodynamic measurements. Information needed to obtain answers for this type of question requires either large numbers of patients whose conditions are comparable, or smaller numbers of patients in whom carefully regulated protocols involving

CARDIOVASCULAR RESPONSES TO DEXTRAN

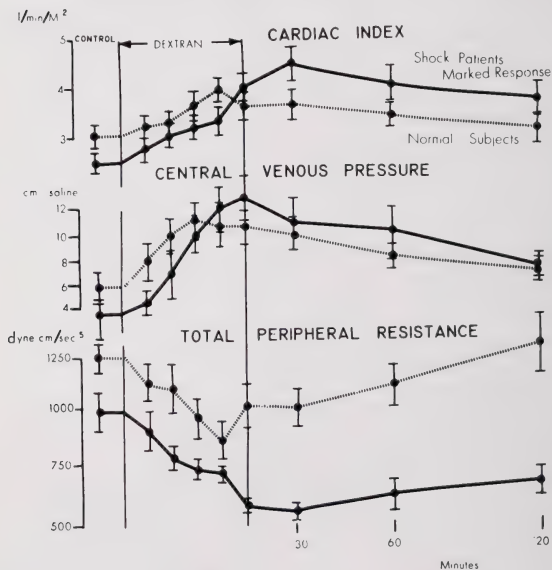


FIG. 8. Hemodynamic responses to Dextran-40 in a series of 6 normal subjects and 24 patients in shock from a combination of hemorrhage, trauma, and sepsis. The time course of changes in cardiac index, central venous pressure and peripheral resistance before, during, and after infusion of 500 ml of Dextran-40 is shown. Dots represent mean values and bars the S.E. of the mean. Data from Carey et al (16) and Mohr et al (17).

CARDIOVASCULAR EFFECTS OF VOLUME THERAPY

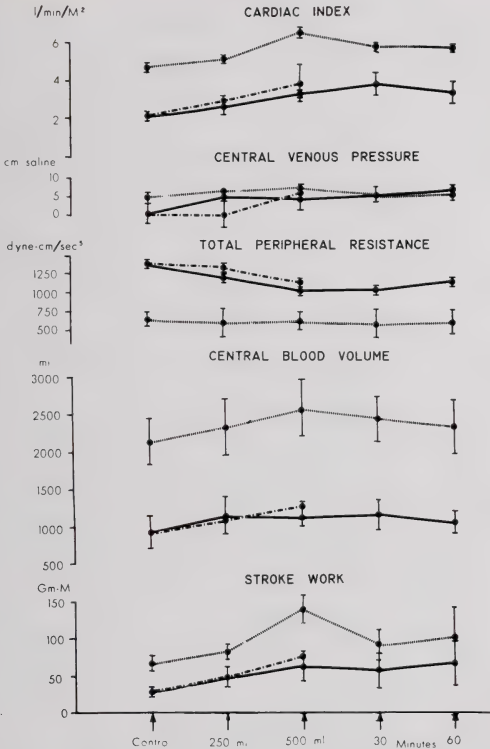


Fig. 9. Cardiovascular responses to volume replacement. Dotted line of each section represents the response of the high cardiac output group to 500 ml whole blood transfusion. Solid line illustrates the response of the low cardiac output group to 500 ml whole blood and the dashed line illustrates the response to 500 ml Dextran-40. No significant difference was observed between the responses of blood and plasma expanders in this acute hypovolemic shock group. (From Monson and Shoemaker (14), with permission of authors and publishers.)

administration of a number of agents given in random order at appropriately spaced intervals. The effects of Dextran-40 administration were studied in shock patients and normal subjects. After Dextran-40 administration, there was elevated central venous pressure increased in cardiac index, reduced pe-

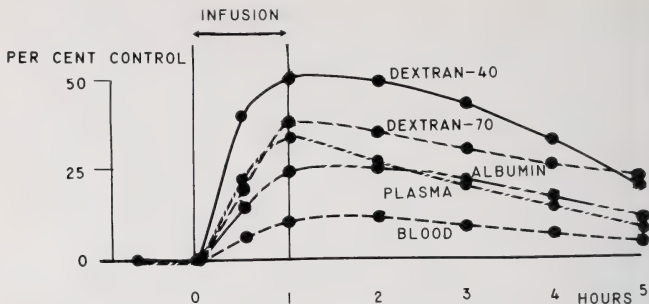


FIG. 10. Time sequence of cardiac output responses to 500 ml of Dextran-40, Dextran-70, albumin, plasma and whole blood given over a one hour period in random order to a series of patients whose blood volumes were normal or near normal. Data from Carey et al (15).

ripheral resistance, and decreased mean transit times (Fig. 8). These effects were most pronounced in patients with severe shock, less pronounced in compensated shock patients and minimal in control subjects (16, 17).

Patients in the hypovolemic stage of acute hemorrhagic shock were given equal volumes of whole blood of Dextran-40. The results (Fig. 9) indicate that these two agents are equally effective in restoring hemodynamic values to normal. By contrast, Dextran-40 produced greater increases in cardiac output than did blood transfusion in a series of shock patients whose blood volumes had been restored to normal. Figure 10 illustrates the comparative responses of whole blood, Dextran-40, Dextran-70, plasma and albumin given randomly in 500 ml volumes over a one hour period. Measurements were made before, during, and after each agent permitting some degree of comparison of the physiologic effects of each agent.

Hemodynamic effects of several sympathomimetic agents were compared in a series of shock patients (18). Differences in the responses are illustrated in Figure 11.

Use of Therapeutic Agents as a Means to Evaluate the Disturbed Circulation

Insight into the essential nature of the disturbed circulation may be gained by planned protocols wherein hemodynamic measurements are used to evaluate in shock patients the effects of specific agents whose action is known. Myocardial function in a series of 23 noncardiogenic shock patients was evaluated by the hemodynamic responses to intravenous administration of Dextran-40 and isoproterenol (17). Studies from this laboratory had shown that Dextran-40 produces a rapid and nearly maximal volume load on the circulation which is reflected by increased central venous pressure in the face of increased cardiac output (16). By contrast, isoproterenol is known to have a

INCREMENTAL CHANGES IN HEMODYNAMICS AFTER SYMPATHOMIMETIC AMINES

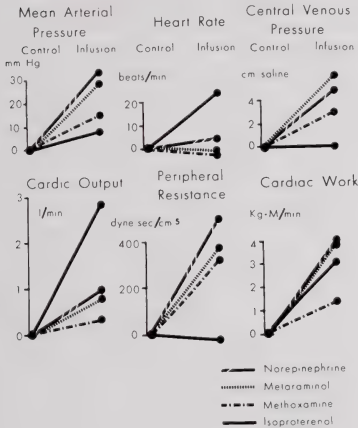


FIG. 11. Changes in arterial pressure, heart rate, central venous pressure, cardiac output, peripheral resistance, and cardiac work in a series of 17 shock patients given constant infusions of norepinephrine, metaraminol, methoxamine, and isoproterenol in random order. The expected responses of the various agents may be matched to the particular hemodynamic deficit of a patient. Also the interactions of the hemodynamic responses of an agent may be seen: e.g. isoproterenol gives the greatest increase in cardiac index relative to the increase in work, and to the decrease in resistance. Data from Brown, et al (18).

direct and powerful inotropic effect on the myocardial muscle. The shock patients could be divided according to cardiovascular responses to these two agents. The first group consisted of 11 patients in whom the cardiac output increased more than fifty percent after volume loading, but did not increase in response to isoproterenol infusion. This suggested that the primary circulatory failure was peripheral vascular failure with limited venous return to the right heart. After dextran infusion the second, intermediate group of patients had moderate improvement in output at the expense of moderate increases in intravenous pressure. The third group (7 patients), in contrast to the first, showed no significant improvement in cardiac output after Dextran-40 but had marked responses to the inotropic agent (Fig. 12).

From this study it was evident that cardiac function was diminished significantly in 7 of 23 patients in shock from noncardiogenic causes. Five patients improved and two ultimately survived after continuous isoproterenol infusion for 12 to 24 hours. Sixteen of 23 patients responded to volume loading. Therapeutic response to volume loading implies that there may have been

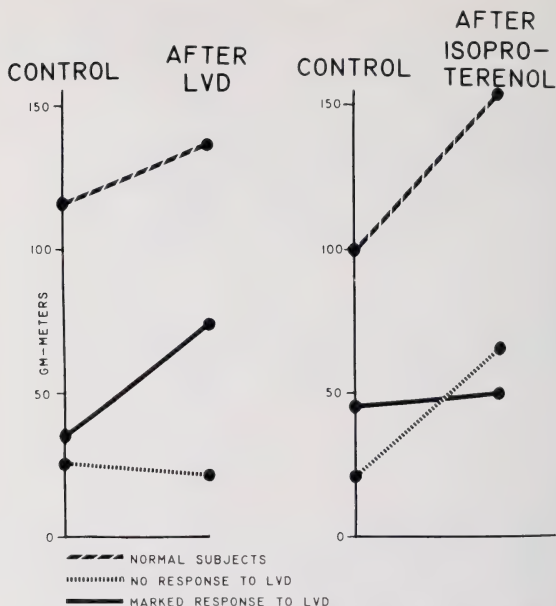


FIG. 12. The left ventricular stroke work response to Dextran-40 (designated here as LVD), shown on the left, and isoproterenol, shown on the right. The responses of 23 patients with shock from combinations of hemorrhage, trauma, and sepsis were compared with responses of 10 normal subjects. Those shock patients who responded well to Dextran-40 (solid line) had minimal response to isoproterenol and those who responded poorly to Dextran-40 responded well to isoproterenol. Data from Carey et al (19).

peripheral circulatory deficiency even though blood volumes were normal or near normal.

Long Range Research Program of a Shock and Trauma Center

The aims of a long range program should include: (a) a search for the significant hemodynamic patterns of the disturbed circulation; (b) definition of the physiologic mechanisms which contribute to the development of acute circulatory problems; (c) identification of compensatory physiologic responses and recognition of the onset of decompensation of these protective mechanisms; and (d) investigation of the hemodynamic and metabolic effects of various therapeutic agents in order to define more precisely their indications and contraindications. Ideally, clinical studies should be conducted in concert with experiments in animal models designed to simulate clinical conditions.

Although a great deal of information has been accumulated in man, most of the data have been confined to isolated measurements which often were made in the preterminal stages. It would seem that the first and most urgent problem is to describe as many of the physiologic alterations as possible throughout the time course of the various types of disturbed circulations. The time of appearance and extent of the alterations may give us needed information to relate the abnormal findings with more primary physiologic alterations. The simultaneous measurement of the course of several physiologic parameters also may aid us in understanding the interaction between the early events and their compensatory reactions. For example, the early findings of increased pulmonary vascular resistance during or preceding arterial O_2 desaturation and high cardiac output may suggest various hypotheses concerning the mechanisms involved in the development of changes in pulmonary function and postshock pulmonary complications. At this point, the early pulmonary resistance changes may be altered experimentally in the animal model to test the hypothesis that increased pulmonary vascular resistance is an important factor in mortality and postshock morbidity.

Similarly the question of the relation of microcirculatory alterations in shock may be approached by photographic documentation of cellular aggregation in the scleral conjunctivae together with observations on the development of changes in cardiac output, peripheral resistance, viscosity changes, pO_2 changes, and O_2 transport. Information derived may lead to a better understanding of the role of microcirculatory alterations in the development of macrocirculatory responses to acute injury.

After background experimental information is in hand, the appropriate and significant observations may be sought in man at the times which would produce the maximum information pertinent both to the patient's medical therapy and the relevant scientific questions.

Table II lists some of the measurable parameters and derived calculations together with the physiologic alterations and mechanisms of death they are presumed to reflect.

Interactions of the metabolic and hemodynamic responses to trauma are relatively unexplored areas. Many of the primary effects of acute illnesses may be metabolic in nature, while hemodynamic alterations may represent compensatory reactions to these. For example, increased cardiac output may occur in response to the body's oxygen needs when there is arterial O_2 desaturation due to anemia, airway obstruction, ventilatory impairment, pneumonia, and other factors leading to failure of oxygen transport across the lung. Thus, in the face of decreased arterial oxygen content, O_2 transport to the tissues may be maintained by increased cardiac output. Moreover, increased oxygen requirements of posttraumatic states may be supplied by increased cardiac output when arterial oxygen content is normal. Correlation of arterial and mixed venous pO_2 values, O_2 consumption, and pulmonary function tests with hemodynamic observations will aid in sorting out the possible mechanisms which may be operative.

TABLE II

Artrial List of Measurements. Derived Values, Physiologic Abnormalities and Possible Mechanisms of Death in the Disturbed Circulation

Direct Measurement	Indirect Calculated Value	Physiologic Abnormality	Mechanism of Death
Volumes Plasma volume, hematocrit, red cell mass	Blood volume, total body hematocrit, hematocrit ratios	Hypovolemia	Hypovolemia, diminished venous return to right heart
Cardiorespiratory Function Cardiac output, heart rate, cvp Cardiac output, mean arterial pressure, cvp pH, pCO ₂	Cardiac work as a function of cvp Peripheral resistance Arterial and mixed venous O ₂ & CO ₂ content; A-V differences and O ₂ consumption, reduced arterial-alveolar pO ₂ difference, pulmonary A-V shunting R.Q.	Cardiac insufficiency and failure Vasoconstriction Metabolic acidosis, respiratory alkalosis or acidosis Reduced alveolar ventilation, arterial oxygen desaturation	Cardiac failure Peripheral vascular collapse Acidosis, alkalosis Failure of tissue perfusion, failure of O ₂ transport
Direct Fick Q ₂ consumption and CO ₂ production EKG Tidal volume, vital capacity, airway and intrathoracic pressure, x-ray	Inspiratory force, pulmonary compliance, pulmonary dead space, airway resistance Hepatic vascular resistance, net rate of hepatic uptake or output of plasma constituents	Arrhythmias Pulmonary ventilatory failure, pulmonary insufficiency Increased hepatic vascular resistance, reduced hepatic blood flow and hepatic function, hepatic glycogenolysis and K ⁺ release	Arrhythmias Miliary atelectasis, massive atelectasis, pneumonia, pulmonary embolus Failure to deliver glucose and other oxidative substrates to peripheral tissues and to clear organic acids
Hepatic and Metabolic Functions Hepatic blood flow, portal & hepatic venous pressures and plasma concentrations as glucose, lactate, pyruvate, K ⁺ , amino acids and lipid fractions			
Renal Function H ₂ N, plasma & urinary creatinine, PAH & inulin concentrations	Creatinine, PAH and inulin clearances	Renal vasoconstriction, reduced renal blood flow, reduced GFR and tubular function Cerebral insufficiency	Acute renal necrosis Cerebral insufficiency, CVA
Central Venous System Function Neurological examination, level of consciousness Systemic Infection Temperature, blood and body fluid cultures Microcirculatory Function Direct microscopy of scleral conjunctiva, C ₂ A red cell equilibration, plasma, whole blood and packed red cell viscosity, coagulation profile		Cell aggregation, intravascular clotting	Sepsis, septicemia Autohemolysis, coagulopathies, hypofibrinogenemia

Low perfusion states lead to incomplete oxidation of glucose as well as accumulation of organic acids, and catabolic breakdown products; each of these latter compounds have pronounced circulatory influences. Simultaneous measurement of the rate of production of organic acids by the peripheral tissues and their rates of removal by the liver will differentiate the extent to which rising plasma concentrations are due to increased production or decreased hepatic removal. Similarly, estimation of the rates of hepatic glucose production may aid in defining the extent to which incomplete oxidation of glucose by the peripheral tissues is attributable to lack of glucose as opposed to limited oxygen availability. In the same manner, the rates of other oxidative substrate movements may elucidate some of the problems involved in energy metabolism.

The use of several approaches which are different from the point of view of methodology may provide more complete descriptions of the nature of the disturbed circulation and the interaction of the various regulatory mechanisms. The hemodynamics of each of the various vital organs, and the neural, hormonal, and metabolic factors that control organ hemodynamics and metabolism may be described and their changes during shock and trauma interrelated. Additional insight into the physiologic mechanisms of the disturbed circulation may be gained by measuring the responses of the vital organs to neural and hormonal stimulation in animals under normal and abnormal conditions. This type of approach may provide information upon which to base hypotheses regarding the genesis of the body's response to stress and the development of the shock state.

Summary

The general background, development, and purposes of a clinical shock and trauma center are reviewed. The problems of monitoring hemodynamic events in posttraumatic and postoperative patients are emphasized.

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Concepts and Treatment in Polymyalgia Rheumatica

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"There is nothing new under the sun," said Solomon (1). Polymyalgia rheumatica appeared to be a new syndrome as, beginning in 1951, reports of such cases accumulated in the British and European literature (2-4). Yet, as so often happens, an astute observation had been published but forgotten, only to come to light long afterward. In 1888, Bruce (5) reported five cases which he named "senile rheumatic gout," but which he recognized as an acute state in the elderly with constitutional illness, and in a category separate from gout and other forms of rheumatism.

Rheumatism in the aged continued to be described, confused and hidden in many guises, as rheumatoid arthritis, osteoarthritis, fibrositis, and undoubtedly as polymyalgia rheumatica. Modern investigators have separated polymyalgia rheumatica from a welter of clinical states, as describing a group of patients with a uniform set of findings, generally good prognosis and prompt response to treatment. Polymyalgia rheumatica has a rapid, often sudden onset of severe pain and stiffness in the muscles of the pectoral and pelvic girdles most frequently of the former. This is accompanied by malaise and depression, a highly accelerated erythrocyte sedimentation rate, and often fever and anemia. Despite the intense pain, stiffness and tenderness, little or no muscular weakness or atrophy develops, joint involvement is absent, and no residua remain on long-term follow-up. Characteristically, the age of occurrence is over sixty years, and the condition primarily involves females. Barber, in 1957, suggested the commonly accepted name of "polymyalgia rheumatica" (6).

It is remarkable that despite the very numerous reports from Britain and Europe, polymyalgia rheumatica was virtually ignored in the United States until 1962, when it was mentioned in an editorial (7); in 1963 a single case report questioned it as an entity (8). In 1966, we reported the initial series of cases of polymyalgia rheumatica in America (9). Interest in the syndrome has since been stimulated, and other reports have appeared (10-12). Simultaneously, there has been increasing awareness, discussion, and controversy over the etiology, pathogenesis, and treatment. In particular, much interest has been directed to the syndrome of temporal arteritis and its relation to polymyalgia rheumatica.

In this communication we will present the clinical and laboratory findings in polymyalgia rheumatica, refer to the differential diagnosis, and discuss our present concept of the approach to the syndrome and its treatment.

Clinical Findings and Laboratory Data

Differential Diagnosis. Polymyalgia rheumatica is confused most easily with polymyositis. The latter, while often presenting without skin lesions, is

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TABLE I
Clinical Manifestations

<i>Onset of Pain</i>	Usually acute
<i>Sites</i>	Muscles of the pelvic and pectoral girdles
<i>Sex</i>	Preponderantly female
<i>Age</i>	Almost always over 60 years
<i>Temperature</i>	Usually elevated slightly to moderately
<i>Stiffness and Pain</i>	Very severe
<i>Muscle Weakness</i>	Minimal to absent
<i>Muscle Tenderness</i>	Minimal to absent
<i>Muscle Atrophy</i>	Absent
<i>Joint Involvement</i>	Absent

TABLE II
Laboratory Data

<i>ESR</i>	Markedly accelerated
<i>Electrophoresis</i>	α_2 and gamma globulin slightly elevated
<i>Hemoglobin</i>	Moderate anemia
<i>Electromyography</i>	Normal
<i>Latex Fixation</i>	Negative
<i>L.E. Preparation</i>	Negative
<i>Muscle Enzymes</i>	Not elevated
<i>Muscle Biopsy</i>	Normal

readily separated by evidence of true muscle atrophy and striking muscle weakness, high serum muscle enzyme levels, myositis on biopsy, and electromyographic changes. The diagnosis of rheumatoid arthritis can only be made when, according to accepted criteria (13), objective joint involvement is present. In addition, one would expect to find rheumatoid factors in the serum. In multiple myeloma, there is bone destruction, myeloma cells are found in the bone marrow, and characteristic serum and urine abnormalities are present. Thorough investigation by x-rays and other studies, plus prompt response to treatment and the passage of time rule out occult malignancies. Similarly, latent infections such as tuberculosis, and the lymphomas, do not stand the test of time, and there are usually positive x-ray and bone marrow findings. Polyarteritis is distinguished by the presence of renal disease, eosinophilia, pulmonary disease, neuropathy, and histological evidence of small artery vasculitis. Systemic lupus erythematosus is usually found in much younger patients, manifests multisystem disease, and lupus cells are almost always found. Fibrositis and peritendinitis are recognized by their localized nature, lack of systemic symptoms, and normal laboratory findings.

The following chart highlights the significant positive and negative findings separating polymyalgia rheumatica from the entities most likely to confuse:

Differential Chart

Polymyalgia Rheumatica	Sedimentation Rate	Joints	Muscle Enzymes
	++	--	--
Rheumatoid Arthritis	++	++	±
Fibrositis	--	--	--
Polymyositis	++	+	++

Discussion

One of the earlier descriptions of elderly patients with the syndrome later to be named "polymyalgia rheumatica" was by Kersely (14). At the same European Congress of Rheumatology, Porsman (15) noted the similarities between such patients and those with temporal arteritis. Numerous reports since then have highlighted differences and resemblances, and controversy as to whether polymyalgia rheumatica and temporal arteritis are part of the same disease is far from purely academic, since the answer directs the therapy.

Among the several schools of thought are:

- Polymyalgia rheumatica is a separate and distinct disease.
- Polymyalgia rheumatica is a variant of "giant-cell" arteritis, a diffuse disease which includes temporal arteritis.
- Polymyalgia rheumatica is an atypical form of rheumatoid arthritis.
- The identical pathogenetic reaction may produce polymyalgia rheumatica, temporal arteritis, or a mixed syndrome.
- Polymyalgia rheumatica is a syndrome of varying etiology and pathogenesis, in some instances related to arteritis, and not so in others.

Several writers have published cases and studies supporting the direct relationship between polymyalgia rheumatica and temporal arteritis (16-20). The evidence is based upon biopsies of the temporal arteries, which in some patients with polymyalgia rheumatica reveal typical "giant-cell" pathology (19-21). Positive temporal artery biopsies have been found where the clinical syndrome was that of polymyalgia rheumatica without clinical temporal artery involvement, and the conclusion has been drawn that all patients with polymyalgia rheumatica may develop, or already have arteritis (21). Since some patients with temporal arteritis have suffered sudden and rapid blindness, the implication has been that this danger must be avoided by appropriate treatment in all cases of polymyalgia rheumatica, namely corticosteroids in high dosage for prolonged periods.

While it is generally accepted that blindness occurs in "giant-cell" arteritis (10, 19, 20, 22, 23), it is rare in polymyalgia rheumatica. As Fessel and Pearson point out, such instances have been noted in isolated case reports (24). We have followed 45 patients, some for over five years. None has evidenced ocular symptoms or impairment, and in one patient only did temporal arteritis develop, but without eye involvement. Other large series of cases of poly-

myalgia rheumatica have been published, three of which total 134 patients, but none with visual disturbances (25-27). Comparison should be made between the absence of visual impairment in such large numbers of patients with polymyalgia rheumatica, and the incidence of twenty percent blindness in temporal arteritis reported in the literature (34). Critical attention must be directed to the proposition that clinical polymyalgia rheumatica and clinical temporal arteritis deal with different patient populations.

As yet, in no instance of polymyalgia rheumatica, whether arteritis is present or not, has any definite clue been elicited explaining etiology or pathogenesis, or the basic clinical signs and symptoms. Muscle biopsies have been uniformly normal; there is complete absence of inflammatory or other alteration in the muscle fibers and blood vessels. In light of this, is it warranted to perform a temporal artery biopsy in every patient with polymyalgia rheumatica? It is generally agreed that arteritis is not present in all instances of polymyalgia rheumatica. Indeed, such cases are in the minority. In addition, patients with extensive cranial arteritis have been found to have normal temporal arteries on biopsy (35). "Giant-cell" arteritis often occurs in "skip areas," so that one would have to take multiple and repeated sections. This is not a very practical approach to the average patient. Certainly, if an individual with polymyalgia rheumatica was discovered to have thickened or pulseless temporal arteries, even scalp tenderness in the temporal area, then the optimum site would be easily noted and the likelihood of a successful biopsy enhanced considerably. Moreover, one can argue that in polymyalgia rheumatica, the physical presence of temporal arteritis should be sufficient to make the diagnosis clinically and to treat accordingly without a prior biopsy.

Treatment. The discussion of the relationship between polymyalgia rheumatica and temporal arteritis is of paramount importance since the method of treatment derives from it. We have noted (9, 28-31) that polymyalgia rheumatica can often be controlled with salicylates, phenylbutazone, or indomethacin. Case reports (32, 33) have indicated the occurrence of serious ocular involvement, including blindness, under such treatment. Therefore, it has been recommended in these reports and elsewhere that large doses of corticosteroids should be used in all cases of polymyalgia rheumatica, whether temporal arteritis is present or not. Corticosteroids do produce spectacular relief and rehabilitation for the patient with polymyalgia rheumatica. But if therapy continues for extended periods, the penalties of long-term, high dosage corticosteroid treatment must be faced, including disturbances of mineralo-glucoid metabolism, osteoporosis, and fractures. These are most pronounced in the elderly. Therefore, in a patient with polymyalgia rheumatica where only a possibility of occult temporal arteritis exists and only the concomitant possibility of ocular damage, doses of 50 to 60 mg of prednisone daily should not be employed indiscriminately. Still, even though only a remote chance of ocular involvement and consequent blindness is present if temporal arteritis is clinically unrecognized, we agree that all patients with polymyalgia rheumatica should be treated with corticosteroids until they are symptom free. We

further believe that when faced with the appearance of temporal arteritis, the performance of a biopsy should not delay the use of corticosteroids, since permanent blindness can strike, even in the few days needed for pathological study. However, we are strongly of the opinion that in the absence of temporal arteritis, minimal doses are to be preferred. Ten mg daily of prednisone or an analog is the initial amount. This may be diminished gradually and in most instances 2.5 to 5 mg daily is an adequate maintenance dose. Steroid-free intervals will determine when a remission has occurred. If temporal arteritis is present or appears, then larger amounts must be employed, but tapered sharply as the arteritis is contained.

We wish to emphasize the clinical distinction between polymyalgia rheumatica with and without attendant arteritis, particularly the temporal variety, for therein lies the path of proper therapy. And lest we tend to lose ourselves in the differential problem of polymyalgia rheumatica and temporal arteritis, we should like to plead for more widespread recognition of the clinical entity of polymyalgia rheumatica. Considerable anguish, expense, and time will be saved many an elderly patient when the diagnosis of polymyalgia rheumatica is promptly made and proper treatment employed.

Summary

From the authors' experience of 45 cases of polymyalgia rheumatica, the clinical and laboratory picture and the differential diagnosis have been outlined. Present day concepts of polymyalgia rheumatica are discussed including its relation to the syndrome of "giant-cell" arteritis and particularly to the subdivision of temporal arteritis. Our views of treatment are considered.

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Tuberculous Mediastinal Adenopathy Simulating Neoplasm

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Introduction

The presence of huge paratracheal nodes in primary tuberculosis is well known and can be seen long after the pulmonary focus has either calcified or disappeared. However, in spite of this, initial consideration in the diagnosis is sometimes directed toward primary or secondary mediastinal tumor and little thought is given to tuberculosis. This is more likely to be the case in the adult, where marked mediastinal nodal involvement in primary tuberculosis is less frequent than in children. We have recently encountered three patients in whom the major manifestation of primary tuberculosis was limited to marked paratracheal nodal involvement. In the first patient, tuberculosis was not seriously considered until neoplastic disease had been eliminated. With this experience, we were able to initially consider tuberculosis in the subsequent cases. Since antituberculous therapy should be instituted as early as possible in the course of tuberculosis, we would like to reemphasize the need to suspect this disease in all cases of marked mediastinal lymphadenopathy.

Evidence substantiating diagnosis of tuberculosis in our patients is as follows: In Case No. 1, a liver biopsy was performed in which a nonspecific granuloma was found. The eventual response to therapy confirmed the diagnosis. In Cases Nos. 2 and 3, the diagnosis was made by discovering acid-fast bacilli in a biopsy—in the second case a supraclavicular node and in the third case, a mediastinal node via mediastinoscopy.

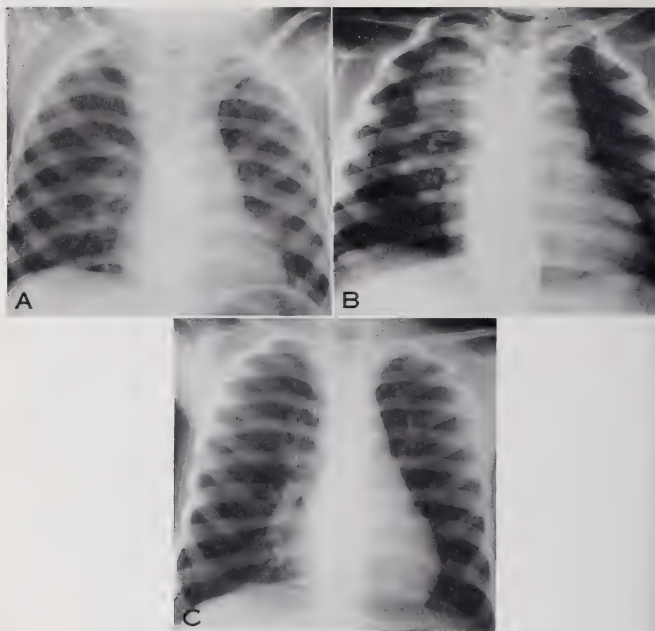
Roentgenographic Features

The main roentgenographic feature of mediastinal tuberculous lymphadenopathy is a single unilateral enlarged paratracheal lymph node that presents on the side of the original pulmonary focus (Figs 1, 2, 3). Bilateral nodal involvement is unusual but can occur with massive infection (2) or when the disease originates on the left side (3). In the latter circumstance, the nodes on the right are frequently larger. Statistically, however, primary tuberculosis more commonly involves the right lung (3) and all three of our patients had enlarged right paratracheal nodes.

An enlarged node has an oval configuration and presents as a localized bulge of the mediastinum (2) (Figs 1, 2, 3). The border is smooth and sharply demarcated by the adjacent lung structure. If multiple nodes are involved, the tumor has a scalloped, irregular border. Simultaneous homo-

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CASE NO. 1

A 4-year-old girl was admitted to the hospital because of low grade fever and hepatosplenomegaly. Because of the subsequent chest findings and a positive skin test, the patient was given INH and PAS.

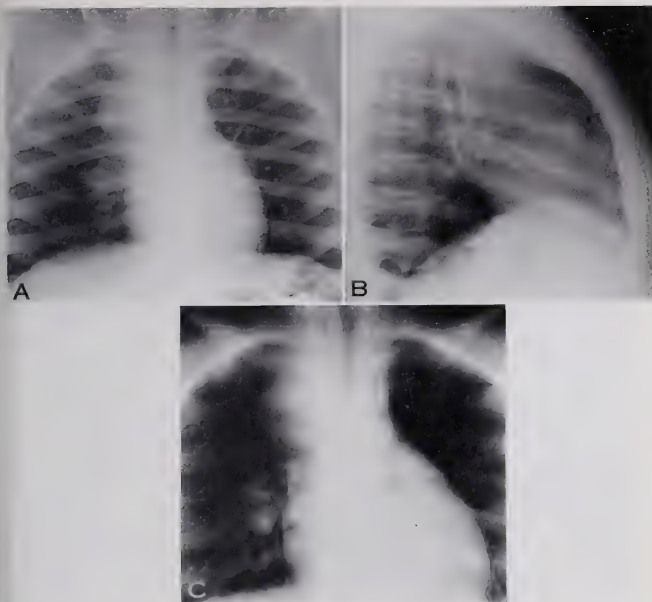
Fig. 1A. Initial chest roentgenogram demonstrates widening of the right paratracheal region. The tumor has an oval configuration and is sharply demarcated. The right hilum appears full suggesting minimal adenopathy in this region.

Fig. 1B. Two months later, the tumor has increased considerably in size. However, therapy was continued and the node regressed slowly.

Fig. 1C. Another chest film taken 4 months after the previous film reveals almost complete disappearance of the tumor. Follow-up films demonstrated no evidence of adenopathy.

lateral involvement of the tracheobronchial and bronchopulmonary nodes may also be present (Fig 2A). However, these nodes are occasionally overlooked because of the marked disparity in size of the paratracheal node.

The diagnosis of tuberculosis should always be considered if and when the pulmonary focus is identified. In most instances, the focus is too small or has already disappeared at the time of the initial examination and differentiation from thymoma, lymphoma, neuroblastoma, metastatic disease, sarcoidosis,



CASE NO. 2

A 12-year-old girl was admitted to the hospital because of fever, cough, and a twenty pound weight loss. Physical examination revealed nothing except a palpable right supraclavicular lymph node. Laboratory studies revealed an elevated sedimentation rate. Tuberculin skin test was positive.

FIG. 2A. Initial chest roentgenogram demonstrates a markedly enlarged right paratracheal tumor as well as a lobular enlarged right hilum.

FIG. 2B. The lateral projection of the chest shows a smooth, rounded parenchymal focus (arrow) at the level of, but presumably medial to an incomplete horizontal fissure.

FIG. 2C. Tomographic cut through the trachea again demonstrates the tumor as well as the right hilar nodes. No definite calcification is seen.

other granulomatous processes, and bronchogenic cyst is necessary. Thymoma and neuroblastoma can usually be excluded on the lateral projection of the chest since they almost never originate in the middle mediastinum. When a single node is enlarged, it is difficult to distinguish tuberculosis from Hodgkin's disease, sarcoidosis, and a bronchogenic cyst. Metastatic disease however, is rarely limited to a single paratracheal node but must be considered when multiple nodes are involved.



CASE NO. 3

A 28-year-old female was referred to the hospital because of a right paratracheal tumor detected on routine chest film. Clinical and laboratory studies were all within normal limits. However, a PPD #1 was strongly positive. The patient received antituberculous therapy and was discharged.

FIG. 3. Roentgenographic examination of the chest during the hospital admission reveals a large, sharply defined right paratracheal mass. No parenchymal lesion is seen.

Discussion

The major pathologic feature of primary tuberculosis is the Ghon complex. The majority of tubercle bacillae migrate to the regional nodes and caseation is more pronounced within the nodes than within the parenchymal lesion. This accounts for the marked enlargement. The symptoms associated with tuberculous adenopathy include fever, malaise, anorexia, and weight loss. These features, however, are also associated with lymphoma and other neoplasms. A tuberculin skin test should therefore be applied in all cases of mediastinal lymphadenopathy and when positive, tuberculosis should be the primary diagnosis. A positive tuberculin test is of major significance in the

pediatric age group. This is also becoming more important in the young adult group since there has been a decrease in the number of positive tuberculin tests in recent years (4). Supplementary studies, if needed, will further exclude other diagnostic considerations. In the adult, it may be necessary to resort to scalene node biopsy, or mediastinoscopy with biopsy to substantiate the diagnosis. The presence of homolateral supraclavicular nodes does not negate the diagnosis of tuberculosis. These were present in the second child and were biopsied to exclude the possibility of lymphoma. Generalized adenopathy usually indicates the presence of lymphoma or metastatic disease.

It is important to recognize that tuberculous nodes may temporarily increase in size during the course of therapy with INH and PAS. This enlargement occurred in the first child (Fig 1B) and by no means contradicts the diagnosis of tuberculosis. Although resolution may require several months, recurrence of nodal enlargement rarely occurs. The addition of steroids to the therapy of tuberculous adenitis is unwarranted. Despite prompt resolution of the nodes with the use of steroids, in the majority of cases adenopathy returns following cessation of therapy and may be more marked than originally (1).

Tuberculous nodes when untreated may ultimately involve the tracheobronchial tree (5). Because of a surrounding periadenitis, the nodes may become adherent to the adjacent bronchus. The bronchial wall may then become secondarily infected and an ulcer or sinus tract may form. Granulation tissue is frequently produced and may cause atelectasis by completely occluding the bronchial lumen. The lymph nodes may also extrude caseous material through the sinus tract into the bronchus causing further parenchymal disease within the lobe. Fortunately with antituberculous therapy, most lesions heal with minimal sequelae. However, when extensive bronchial damage has occurred prior to the onset of therapy, healing occurs with scarring and resulting bronchiectasis. Obstruction of the tracheobronchial tree by tuberculous lymph node compression without actual involvement of the wall is rare.

Because extensive caseation transpires within the regional nodes, calcification develops more often at this site than within the primary focus. Calcification is usually minimal if extensive caseation has not occurred prior to the onset of medication. In general, calcification occurs more rapidly in the younger individual and may require years in the adult. Calcified nodes are almost always clinically insignificant. However, occasionally they erode through the adjacent bronchus forming a broncholith causing obstruction many years after the primary infection.

Summary

Primary pulmonary tuberculosis is occasionally associated with huge mediastinal lymphadenopathy with or without the presence of a parenchymal focus. Because of this, tuberculosis may sometimes be omitted from the initial differential diagnosis, especially in adults. Since early institution of anti-

tuberculous therapy is desirable, it is imperative to suspect tuberculosis in all cases of mediastinal adenopathy.

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Wrist-cutting and Suicide

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The authors have encountered with increasing frequency patients with a presenting problem of "wrist-cutting," a phenomenon which we believe constitutes part of a new clinical syndrome (1-3). We include in the category of "wrist-cutting," any self-inflicted wound of the wrist (other body parts are sometimes mutilated—see Case I), from a superficial "scratch" to an actual penetration of the skin and fascia. The patient is almost invariably a female who is brought to the physician after she has cut or scratched her wrists in what appears to be a suicide attempt. Frequently the question of hospitalization is raised. Greater experience with these young women, however, suggests that they present a unique clinical entity, presenting difficult diagnostic and treatment problems. The apparent suicidal intent of these patients, though, may be better understood as part of a total pattern of functioning rather than as a serious threat to life.

The Mount Sinai Hospital of New York, Institute of Psychiatry is a voluntary, open-ward hospital with about a hundred and twenty inpatients hospitalized for acute illnesses who remain for an average of six to twelve weeks. Over the last two years more than forty patients in this institute have been hospitalized because of repeated wrist-scratching (4). The vast majority have been young females, diagnosed as borderline or schizophrenic, whom we have loosely categorized as "anhedonic" (5). Glauber used this term some years ago to describe patients who "fear ego impoverishment and annihilation" (6). They are devoid of meaningful object relations, fail to find pleasure without the strongest stimulation, and complain readily and spontaneously of severe feelings of emptiness. Typically, they are girls ranging in age from 15 to 23 (males are rare), give histories of intense loneliness and boredom and inability to concentrate in school despite above-average intelligence. Their fluid and unstable social lives usually involve frequent and varied drug use and frequent and unrewarding sexual encounters. Much of this behavior is common to disturbed adolescents, but these patients show a remarkable absence of guilt about their actions, not defending it, but merely regarding it as necessary. Finally, all of this behavior might be regarded as a desperate search for *stimulation*, with an increasing pressure of activity leading to a crescendo of apparent hedonism involving sex, sky-diving, or LSD trips, in short, acts which are poor disguises for self-destruction but quite obviously "thrilling" (4, 5). Two patients, in treatment with the authors, well illustrate this pattern.

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Case Reports

Case I. C.S. is a 17-year-old white female college freshman, brought to the hospital by her mother who requested hospitalization for her. The patient's mother, a biological scientist complained of finding birth-control pills in the possession of her daughter. When she confronted her daughter with her discovery, it became known that the patient had been having regular sexual experiences since the age of 14. In addition, she admitted to using marijuana and amphetamines for about the same period of time. The discovery and confrontation caused great friction and both verbal and physical fighting in the home. The mother and father, who is an attorney, decided that their daughter was sick and required hospitalization.

C. is a plain-looking, frightened adolescent who looks somewhat older than her years. She was guarded, evasive, and expressed no desire for treatment. She said, "There is nothing wrong with me, I just want to be away from my parents."

Within a few weeks of inpatient treatment, C's controlled facade no longer masked the turmoil of her inner life. She gained more trust in the therapist and began to reveal the pains and frustrations of her past and present life situation. She described feelings of "emptiness," "feeling dead inside," profound loneliness and "detachment." She described periods of what were probably depersonalization. C. talked of her frantic attempts "to feel better" by using drugs and her attempts at sexual intercourse "to become closer to another person." These attempts were only partially successful.

After three weeks of hospitalization C scratched her legs for the first time, an action she repeated on at least twelve occasions. The first mutilation was done on the anterior surfaces of both legs, with a tweezer and consisted of about two dozen superficial lacerations done in a criss-cross fashion.

The precipitating event was not clearly understood, but seemed related to an interchange with her mother in which she was told she was "weak" and "acting foolishly." Subsequent episodes seemed less causally defined, but in general were related to strains in her relationship with important people in her life, e.g. mother, father, younger sister, and boyfriend. About all these incidents she said, "My legs were always the ugliest part of me, and I want to make them really ugly." She always achieved some relief with the cutting, a relief from feeling "dead," "empty," "like a leech."

C. was an inpatient for four months. Despite numerous incidents of leg scratching, thigh and wrist scratching, it was our feeling that progress was being made. Paradoxically, we considered the symptoms of self-mutilation in this patient a meaningful step towards more mature ego functions and ego autonomy. Since her discharge one year ago, there have been two incidents of mutilations requiring brief hospitalization of from two to five days. She has returned to school and is living apart from her parents.

Case II. D.B. is an 18-year-old white Jewish girl high school student who entered The Mount Sinai Hospital of New York, Institute of Psychiatry when her private psychiatrist suggested that her frequent self-mutilation required hospital treatment. She began psychotherapy about a year prior to admission when she cut her wrists for the first time. She entered the hospital reluctantly, failing to understand why others found her wrist-cutting so disturbing.

She appears to be a charming, articulate and intelligent adolescent who described apparently normal social and intellectual functioning. She had experimented with marijuana on a few occasions and has had little sexual experience. Not until she was directly questioned did she reveal the existence of a well-constructed delusional system and constant hallucination in every sensory area. She claimed to be in touch with a complete "internal kingdom," replete with gods, goddesses, and demons, who spoke in a secret language. She had lived in this kingdom since early childhood and retreated to it whenever her earthly life seemed unpleasant. The parallel between this system and the elaborate internal fantasy world described in Hannah Greene's *I Never Promised You a Rose*

Garden (which this patient has never read) is striking. Equally striking is the similarity to the patient described therein, she was also a wrist-cutter (7).

Little in her family background explains the development of symptoms so severe. Her parents, both in their early forties, had weathered many years of a stormy but intact marriage. Her mother, a housewife, experienced repeated severe depressions requiring psychiatric treatment but was never hospitalized. Her father, a highly successful executive, was frequently away on business trips but presented himself as a model parent. A brother, two years her senior, had a brief psychiatric hospitalization for barbituate overdose about a year before the patient's admission. Although one may trace the rudiments of the patient's psychotic system to her sixth birthday, the family is unanimous in describing her development as unremarkable in any way.

The patient was hospitalized intermittently at Mount Sinai for about 18 months; during this period she was treated by her private psychiatrist and resident physician as co-therapists. She cut her left wrist and arm more than thirty times, requiring sutures on several occasions. But as attempts were made to explore her reasons for doing so, it became increasingly clear that the lacerations were not intended as suicide attempts. Rarely, they followed command hallucinations, directions from the internal world to punish herself for some imagined sin. More often, though, they occurred when the patient feared she would lose touch with reality entirely. Typically, she would describe a feeling of increasing remoteness and emptiness ("I felt wrapped in cotton wool, with things getting farther and farther away") and would cut herself, and go on cutting, until she felt more touch with her environment. She was quite explicit in describing the value of cutting as a defensive maneuver, explaining that the sight of her own blood often prevented a retreat into a remote and terrifying world of fantasy.

Despite intensive psychotherapy and high doses of phenothiazines, there was little change in her clinical status. But as the psychiatric staff became more aware that her self-mutilation presented little threat to her life, treatment became more flexible and she was allowed more privileges, such as passes, and was ultimately discharged. Because the underlying psychosis seems amenable only to long-term, intensive psychotherapy, she will shortly be admitted to a hospital providing such treatment. In the interim, though, she seems able to function fairly comfortably outside the hospital.

Discussion

Although our primary purpose is to demonstrate the existence of a clinical syndrome of wrist-cutting in anhedonic young females, the physician will be understandably concerned with the suicidal risk involved in such a gesture. A moment's reflection on anatomy will reveal that this is an unusually difficult way to draw large amounts of blood. In 1963, 417 persons, about two percent of all suicides, died after cutting their wrists (8). Repeated surveys of The Mount Sinai Hospital inpatient population show that between 5% and 20% of psychiatric patients have a presenting problem of "wrist-cutting," suggesting that though wrist-cutting is a common cause of alarm, it is rarely life-threatening. Graff, surveying twenty young women with symptoms similar to those described here, suggests that frequent wrist-cutting in no way portends marked suicidal potential (2).

The patients surveyed here display many similar features. Common to the syndrome are severe disorders of ego functioning, reflected by disturbances in object relations, distortions of body image, and failure to identify with any significant person in early childhood, with resultant poor judgment, chronic depression, and complaints of "emptiness." Understandably, these

patients are subject to episodes of depersonalization with concomitant anxiety. Handicapped by their inability to refer to a meaningful introject or an important external object, these girls reject the Cartesian maxim "I think, therefore I am" and revert to the more primitive but reliable "I feel, therefore I am." Confronted with anxiety or depression they affirm the integrity of their body and ego by the most concrete means, by proving that a person who bleeds is alive and will be cared for. In more extreme cases, blood alone is enough to establish a sense of bodily integrity. In others, the dutiful attendance of doctors and family affirms that many important persons care for her.

Summary

A new syndrome, consisting of repeated wrist-cutting in young females who are frequently schizophrenic and often described as "anhedonic," is described. Two cases, which illustrate the syndrome and suggest that wrist-cutting does not portend suicide, are presented. Wrist-cutting is described as a symptom which occurs with increasing frequency and is most prevalent in young women whose apparent suicide attempts are in fact efforts to avoid depersonalization or psychosis: the personalities of such individuals are briefly delineated. Suicidal risk in such patients is felt to be minimal. In the syndrome recognized, understanding of the underlying psychodynamics and the meaning of the symptom in this context is felt to be far more important than the gesture itself.

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The Bassen-Kornzweig Syndrome:

18 Years in Evolution

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The Bassen-Kornzweig syndrome, first described in 1950, has, over the past eighteen years, become a well-documented clinical entity, with implications for general medicine which vastly overshadow its relative infrequency of occurrence.

The fundamental mechanisms which form the basis of the Bassen-Kornzweig syndrome have been better elaborated in recent years. The protean clinical manifestations of the syndrome have been drawn together into a meaningful pathophysiologic pattern.

In 1950, Bassen and Kornzweig (1) described a neuromuscular disorder resembling Friedreich's ataxia, associated with atypical retinitis pigmentosa and a malformation of erythrocytes. The original case described was an 18-year-old Jewish girl, the oldest of three siblings, who was referred for diagnostic studies to the Consultation Service at Mount Sinai by Dr. Kornzweig because of unusual neurologic and ophthalmologic findings. The picture in general was thought to conform to Friedreich's ataxia, with an atypical type of retinitis pigmentosa, and was considered to be of an hereditary nature related to consanguinity in that the parents were first cousins. In the course of a routine blood count, the red blood cells exhibited unusual abnormalities in shape.

Ophthalmological examination of the girl showed the entire retina in both eyes to be of an abnormal color, with pigment disturbance of a "washed-out" character. In the macular region, there were irregularly depigmented and pigmented and silvery glistening patches. In the midperiphery, pigmentary degeneration and proliferation were seen of the typical bone-corpusele and clumped type (Fig. 1). There was a moderate general contraction of the fields of vision, most marked in the upper nasal quadrants. A large ring scotoma was present and a relative central scotoma of 5 degrees. The blind spot could not be defined (Fig. 2). Color fields could not be elicited. Vision was markedly reduced to 20/100 in both eyes. The ophthalmologic picture was that of an atypical retinitis pigmentosa with involvement of the macula in the degenerative process. There was an oscillating nystagmus of the type seen in individuals with poor fixating mechanisms, as indicated by the macular disease.

Neurological examination showed: 1. An ataxic, unsteady gait. 2. Ataxia of all extremities, increased when the eyes were closed. 3. Intention tremor in both upper extremities, with loss of cheek (Gordon-Holmes rebound phe-

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FIG. 1. Drawing of the fundus of the right eye. The optic disc was slightly paler than normal, but the margins were clear and sharp. The arteries were narrowed. Surrounding the disc and in the macular region were glistening areas with a greenish tint. There were pigment deposits in the macular region of a clumped brownish type. In the midperiphery, especially along the blood vessels, were numerous deposits of black pigment of the typical bone corpuscle type. The picture is that of pigmentary degeneration of the retina with macular involvement.

nomena). 4. Loss of ability to perform discrete, individual finger movements bilaterally. 5. No focal atrophy, but the legs were slender and showed moderate weakness. 6. The deep reflexes were not elicited on ordinary testing, but when the legs were allowed to dangle, patellar tendon stimulation gave a pendular response on the right; the abdominals were present but easily exhausted. There was a left Babinski and an abnormal plantar response on the right. 7. Position sense was almost lost in the toes and impaired in the fingers; vibratory sense was lost except in the most proximal part of each extremity. Touch was impaired in the stocking area bilaterally. 8. The patient had many so-called stigmata of degeneration: epicanthal folds, curving of little fingers, incipient Dupuytren's contracture, highly arched palate, and male type of pubic escutcheon. The opinion was that the patient had diffuse disease of the central nervous system involving the posterior columns, pyramidal tracts, and cerebellar pathways. The nystagmus was felt to be related to the disturbance in the fixation mechanism. The picture was that of Friedreich's ataxia, a condition often associated with congenital abnormalities.

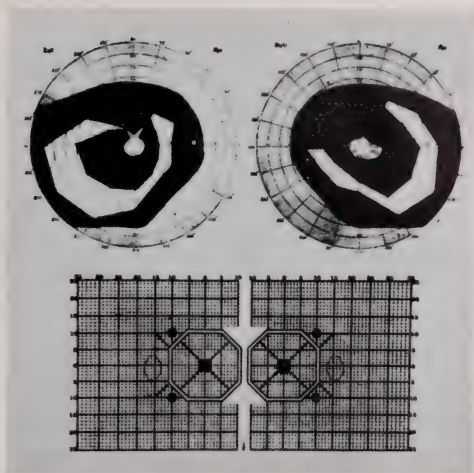


FIG. 2. The peripheral fields of vision (upper figure) show a generalized contraction and a large ring scotoma which almost completely encircles the central region. The only part of the field that was visible to the patient was the central clear area and the strip of clear area to the side. In the lower figure, which represents the central fields, there is a central scotoma which measures somewhat less than 5 degrees. This is represented by the black spot in the center of the field. It was difficult to measure this with great accuracy because of the nystagmus of the patient.

Hematologic findings disclosed a most unexpected picture. The count in general was quite normal except for a slight anemia (Table I). Great numbers of stained red cells, however, revealed unusual abnormalities in shape and to some extent in size (Fig. 3). In general, they presented a crenated appearance, but of such a degree that they took on bizarre shapes simulating small beetles, crabs and turtles; others were star-shaped. The variations depended on the number and length of what appeared to be appendages growing out of the cells. Some of the cells appeared small and deeply stained; they resembled spherocytes from which buds or pseudopods were protruding and these cells in particular varied from ordinary crenation. These peculiar distortions were most marked in the centers of the blood films; towards the periphery the cells generally appeared more normal, although here, there was a marked variation in size. The smaller cells in these thin areas presented in addition a spherocytic appearance, and, occasionally, one of these cells would show the presence of a small appendage indicating incipient distortion.

Another finding was the complete absence of rouleaux formation. Wet preparations revealed the same abnormalities. The red cells appeared abnormal on immediate examination and no progressive changes were noted.

TABLE I
Hematologic Findings

<i>Blood Count</i>		
Hemoglobin.....	78 per cent (11.3 Gm.)	Neut. Non-Seg..... 2.0
Red Cells.....	3,890,000	Neut. Seg..... 54.0
White Cells.....	5,650	Eosinophiles..... 1.0
Platelets.....	190,000	Basophiles..... 1.0
Color Index.....	1.0	Lymphocytes..... 29.0
Hematocrit.....	40.2	Monocytes..... 3.0
Mean Corpuscular Volume.....	103	Reticulocytes..... 2.0
<i>Bone Marrow</i>		
Nucleated Cell Count: 150,000/cu.mm.		Megakaryocytes: 110/cu.mm
Myeloblasts.....	0.5	Lymphocytes..... 4.0
Myelocytes Neut.....	19.0	Hematogones..... 5.0
Myelocytes Eos.....	1.0	Erythroblasts..... 1.0
Neut. Non-Seg.....	21.5	Normoblasts..... 32.5
Neut. Seg.....	15.0	
<i>Saline Fragility Test</i>		
No hemolysis.....	0.72-0.48	
Partial hemolysis.....	0.44-0.04	
Heat Resistance Test: Negative		
Exposure of red cells to cold agglutinins plus tapping:		
Increased resistance as compared to normal red cells		
Anti-human globulin test: Negative		

(From Bassen and Kornzweig, Blood, 5(4):381, 1950.)

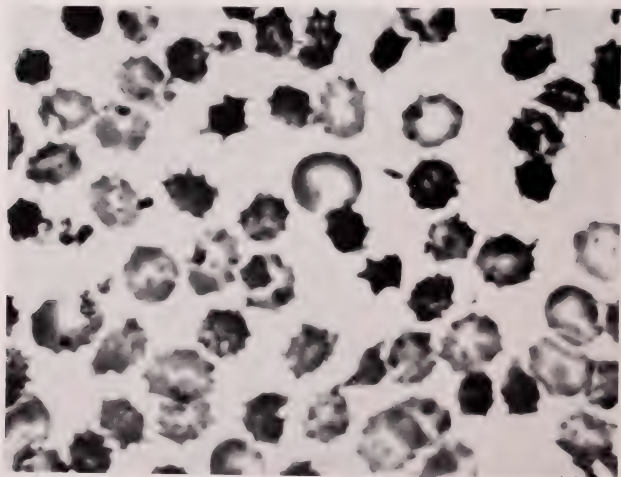


FIG. 3. Note the generally crenated appearance of the red cells and the variations in size. The smaller, deeply stained cells resembling spherocytes undergoing crenation stand out sharply.

In a counting chamber, with 4% sodium citrate as a diluent, the cells appeared normal. The fragility of these cells was tested using hypotonic salt solutions, and their resistance was found to be slightly increased (Table I). This increased resistance was noted too, using the principle of exposing cells to cold agglutinins and shaking, as described by Stats.

The sternal marrow showed slightly increased erythroid activity; otherwise no abnormal findings were noted.

It seemed likely that consanguinity played an important role in the development of abnormalities in the affected sister and brother in this family. The occurrence of a similar condition in sister and brother indicated an hereditary trait occurring as a recessive characteristic and manifesting itself with consanguinity. The third sibling, a normal sister, may have been heterozygous for the recessive gene or completely lacking.

The association of atypical retinitis pigmentosa with Friedreich's ataxia had been reported by Kapuscinski in 1934 and with cerebellar ataxia by Biemond in 1934. These conditions always appeared as a recessive hereditary characteristic, which seemed to be the situation in the present case.

Shortly afterward in 1952 Singer, Fisher and Perlstein (2) reported a remarkably similar case and gave the descriptive term of *acanthrocytes* to the abnormal red cells. They derived the term etymologically from the Greek word "*acanthous*," meaning spiny. The parents in this case were second cousins and also apparently normal in all respects. In both cases, there was an early history of celiac disease with steatorrhea, and the neurological changes were similar. In Singer's case, however, there were no retinal changes, at first.

In 1957, Kornzweig and Bassen (3) reported on the brother of their original case. When abnormal red cells were first discovered, there were minimal ocular changes but no other noteworthy finding. However, during the seven year period, the disease progressed. Ophthalmologically, the optic discs were paler and the retinal vessels were narrowed. Pigmentary degeneration had advanced so that it was readily seen in midperiphery (Fig. 4). The fields of vision showed a complete ring scotoma in the right eye and a partial ring scotoma in the left eye (Fig. 5). Vision with correction was still 20/30 in each eye, although the patient now had compound myopic astigmatism. He had been operated on for a right exotropia, apparent in 1950, but which had become progressively worse during the intervening years.

On neurological examination, his ataxia had progressed to the point where he could no longer attend school and had to get instruction at home. He was increasingly clumsy in the use of his hands, stuttered increasingly, and suffered from weakness of the urinary bladder. Neurological examination revealed progression of all the neurological findings: There was inability to arise with ease from a reclining position; the gait was waddling and unsteady; there was marked lordosis and prominence of the abdomen; there was wasting of the muscles around the shoulder girdle and upper and lower extremities; there was weakness of the muscles in all extremities, trunk and neck. All the deep reflexes were absent and could not be obtained with reinforcement. There

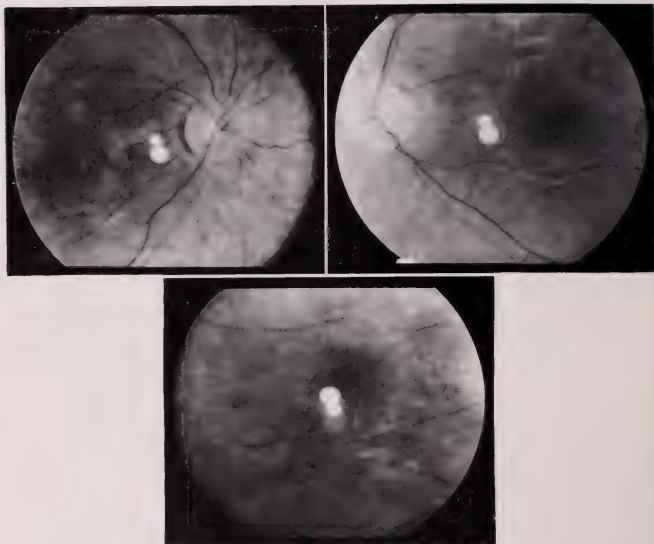


FIG. 4. Fundus photographs of the right and left eyes showing the pallor of the disc and the marked narrowing of the retinal arteries. In the lower photograph, a section of the midperiphery is seen with a spot of pigmentary degeneration.

was a positive Romberg sign, ataxia in the performance of the heel-to-knee test, and some ataxia in the finger-to-nose test. Dysdiadokokinesia was evident in both upper extremities. Vibration sense was very much diminished to absent in all four extremities. Position sense was impaired in the toes. There was glove and stocking type of hypesthesia. The speech was progressively nasal; hearing was slightly defective for high tones (Fig. 6).

In summary, it was the opinion of the neurological consultant, Dr. Morris Bender, that the patient had an heredito-degenerative neuromuscular disorder, with signs of diffuse myeloneuropathy and progressive muscle dystrophy. The etiology appeared to be familial.

Hematological studies showed no change since the original observation. He still had the same peculiar type of red blood cells, the so-called acanthrocytes, checked repeatedly through 1956 and 1957, eight years after the original observation.

An electroretinographic examination of the entire family was done by

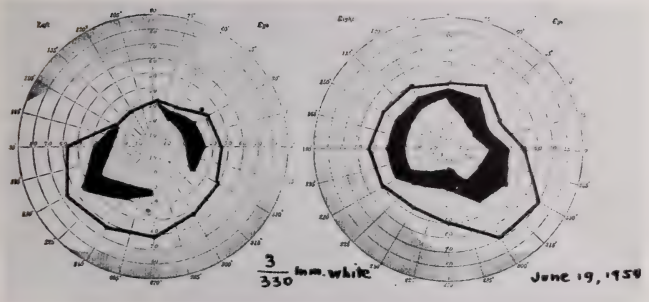


FIG. 5. Peripheral fields at the age of 15 years, showing a complete ring scotoma in the right eye and a partial ring scotoma in the left eye.



FIG. 6. Posterior photograph illustrates kyphoscoliosis, thin habitus, and inability to stand alone. A. photograph illustrates exaggerated lordosis and inability to stand alone. B. facial appearance. There is bilateral ptosis, but ocular movements are normal. (From Schwartz, et al, Arch Neurol 8:434, 1963.)

Dr. J. Jacobson at the N. Y. Eye and Ear Infirmary and revealed a complete absence of electrical response in the two affected children and a normal response in the parents and remaining child.

This then was the third case reported of a rare hereditary disorder characterized in all three by early celiac disease, progressive ataxic neuropathy, and a peculiar malformation of the red blood cells. Two of the cases reported were brother and sister, and the parents were first cousins. In the third case, the parents were second cousins. It was believed, therefore, that consanguinity played an important role in the development of this unusual condition. The development and course of this disorder were remarkably similar in the three cases with the important exception, however, that there were no retinal changes in the case when reported by Singer, et al. In the brother and sister, retinitis pigmentosa occurred, without macular involvement in the boy and with macular degeneration in the girl.

In 1958, Jampel and Falls (4) reported an extremely interesting follow-up of the patient of Singer, Fisher and Perlstein. The patient showed continued progression of ataxia, intention tremor, and involuntary movements by 1956. Over a period of about three years, he had become aware of a gradual deterioration in his vision as well as the neuromuscular defects; a definite intellectual decline was noted by his parents too. Neurologic examination by 1956 revealed a chronically ill, 19-year-old white youth; he was unable to speak and would respond to questions by nodding. His head was tonically turned to the right. Periodic involuntary, bobbing, dystonic movements of his head were noted and were exacerbated when the patient was subjected to stress. The upper extremities exhibited similar involuntary movements with an athetoid quality. There was marked cerebellar ataxia involving all four extremities. Volitional movements of the lower extremities were so uncoordinated that the patient could neither stand nor walk. The muscle tone was generally decreased and the deep tendon reflexes were suppressed. Motion, position, and vibratory sense could not be elicited up to the level of the clavicles. The general physical examination showed gonadal atrophy.

The ophthalmic examination showed a maximum visual acuity by this time of 20/400 in both eyes with correction. The patient could not read the largest Jaeger type. The pupillary reflexes were normal. There was associated nystagmus on right and left lateral gaze. The point of basal convergence was poor. Ophthalmoscopic examination revealed clear media bilaterally; the optic papillae were sharply outlined and normal in size and shape, but they had a definite waxy yellowish pallor (Fig. 7). They contained physiological depressions but no visible lamina cribrosa. There was bilateral peripapillary chorioretinal atrophy. The retinal arterioles and venules showed a marked diffuse attenuation. The retinal peripheries were highly tessellated. In the intermediate retinal areas, there were many glistening highlights having a distinct gelatinous shagreen, and the deep pigment in this area was characterized by disorganization and definite clumping. However, there was no typical bone corpuscular pigment configuration. In the macular areas of the

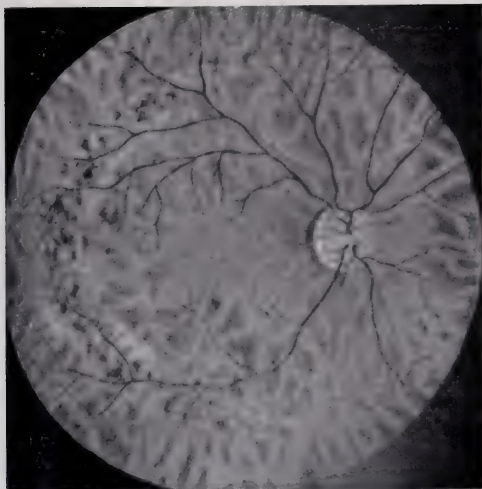


FIG. 7. Drawing of fundus. Fundus photography was precluded by nystagmus. The artist has attempted to illustrate the following characteristics: A waxy-appearing disc, attenuation of the venules and arterioles, disorganization of the deep pigment in the midperiphery overlaid by glistening highlights, and a distinct gliosis of the macula. (From Jampel and Falls, *AMA Arch Ophth* 59:818, 1958.)

retinae, the foveal reflex was not visible. There was a distinct gliosis of the internal limiting membrane. The visual fields were irregularly contracted to approximately twenty degrees with a 3/330 white test object. No annular scotomas could be demonstrated.

Laboratory and chemical findings of note were: 1. Blood: Hemoglobin—13.8 grams or 85%; red blood count—5 million; "thorn-like" cells with irregular projections were present in large numbers, that is to say, the so-called acanthocytes. White blood cells 5900, normal differential count. 2. Urine and stool—normal except for high stool fat content. 3. Blood cholesterol—total cholesterol 37 mg%, cholesterol esters 23 mg%, free cholesterol 14 mg%. 4. Free-flowing electrophoresis: Analysis of the serum protein by free-moving boundary electrophoresis by the Tiselius technique revealed the following findings: The albumin and alpha-1 and alpha-2-globulins were normal; there was a low gamma-globulin and a low beta-globulin value. The decrease in the beta-globulin fraction was interesting in view of the fact that, in this patient, a low total cholesterol value was found. In general, this fraction of serum globulin reflects cholesterol levels of the serum.

In conclusion then, Jampel and Falls noted that the patient of Singer's had,

over the years, indeed developed retinitis pigmentosa, in addition to the acanthrocytosis and neuromuscular disease, presumably hereditodegenerative. He then had the complete Kornzweig-Bassen syndrome. A feature which Jampel and Falls observed for the first time was the phenomenally low serum cholesterol values, one of the lowest ever recorded at their institution.

They concluded that the entire syndrome is basically an inborn error of fat metabolism, producing a harmful effect on erythrocytes and nerve cells. They suggested that careful blood studies may be indicated in unusual cases of retinitis pigmentosa.

Another case of acanthrocytosis was described by Druetz (5) in 1959. A woman, aged 30, whose grandparents were first cousins but whose parents were unrelated, showed a nonpigmentary retinitis with choroiditis. She was said to have been ataxic from the age of two years. Druetz's patient, like the two patients reported by Kornzweig and Bassen and the patient of Singer et al, suffered from celiac syndrome. Druetz's patient had had diarrhea in infancy and, at the age of 30, she was very thin, suffered from episodes of diarrhea, and complained of "fat intolerance." Her serum cholesterol, like the patient of Singer reported by Jampel, was also markedly reduced, namely 60 mg/100 ml. Druetz suggested that the term acanthocytes would be more correct without the letter "r."

In 1960, Salt, et al (10) reported an additional case of the same clinical symptoms. They termed their paper: "On Having No Beta Lipoprotein: A Syndrome Comprising A-Beta-Lipoproteinemia, Acanthrocytosis, and Steatorrhea." Their investigation of the defective fat absorption and transport made it possible for them to enlarge the previous concept of the syndrome. The case of Salt et al was a 17-month-old girl with steatorrhea of severe proportions who was found upon exhaustive laboratory and chemical investigations to have no serum beta-lipoprotein, with corresponding lowering of cholesterol (22 mg/100 ml) and phospholipids (45 mg/100 ml). No particulate fat (chylomicrons) appeared in the plasma after a fat meal. Plasma vitamin A was grossly deficient, and the carotenoids were absent. Further investigation of the steatorrhea excluded celiac disease and fibrocystic disease of the pancreas. Her red blood cells showed the phenomenon of acanthrocytosis like the patients with the Kornzweig-Bassen syndrome.

In the parents and one grandparent of Salt's patient, the beta-lipoprotein was reduced to about half its normal level. Salt, et al are of the opinion that the syndrome they designate as A-Beta-Lipoproteinemia is an inborn error of metabolism with a recessive mode of inheritance. The mutant gene is transmitted as an autosomal recessive. That, of the five patients reported, three were the offspring of consanguineous marriage suggests that the defect is an extremely rare one.

The primary gene effect appears to be an inability to form the beta-lipoprotein molecule and is probably concerned with the protein moiety. As a result, beta-lipoprotein is absent in the homozygote and, in the heterozygote,

it is reduced to about half the normal level. Correspondingly, cholesterol and phospholipids of the serum are reduced.

With respect to the acanthocytosis, Bassen-Kornzweig, Singer et al in 1952, and Druez in 1959 had described the features of the red cell abnormality in detail. In all cases, this had been confined to the homozygote. Druez suggested that the acanthocytosis may result from an abnormal structure of the red cell membrane or from an abnormal binding of the lipoprotein molecules to the underlying hemoglobin.

Salt, et al suggest two further hypotheses which could link the A-Beta-Lipoproteinemia and acanthocytosis: 1. A missing enzyme which is responsible for the absence of beta-lipoprotein from the plasma may also interfere with the formation of a protein or lipoprotein essential for normal red cells structure; or 2. Beta-lipoprotein may be essential for the transport of some substance needed for synthesis of the red cell envelope.

As for the ataxia and atypical retinitis pigmentosa, Salt, et al favor Singer's view that these disturbances are genetically determined. They speculate that the factor essential for the production of beta-lipoprotein is also essential for the normal structure and function of nerve cells. However, the possibility that these disturbances result from disordered fat absorption and transport cannot be completely ruled out. They note that absorption of vitamin A is impaired whenever chylomicron absorption is interfered with; and the carotenoids, the precursors of vitamin A, are normally carried in plasma by beta-lipoprotein. It is, therefore, not surprising that, in the patient of Salt et al, serum levels of vitamin A were low and carotenoids absent; it is conceivable that prolonged severe vitamin A deficiency can play a part in the causation of the ataxia and retinopathy, too. Administration of water-soluble vitamin A raised their patient's serum level to normal; whether in this way the distressing neurological features in the syndrome could be prevented remained to be demonstrated.

In regard to the steatorrhea, the outstanding feature of the fat absorption defect in Salt's patient was the complete failure of particulate fat (chylomicrons) to appear in the blood after a fat meal. They suggest that until more exact knowledge of the protein moiety of chylomicrons and other lipoproteins is available, three alternative hypotheses could explain the absence of chylomicron from their patient's serum: 1. An enzyme essential for the formation of beta-lipoprotein may likewise be essential for the formation of chylomicron. 2. The presence of beta-lipoprotein within the cell may be necessary for the formation of chylomicrons from triglyceride. 3. The presence of beta-lipoprotein in plasma may be necessary for the maintenance of the chylomicron emulsion.

They emphasized that the diagnosis of A-Beta-Lipoproteinemia should be suspected in a patient with steatorrhea associated with a very low serum cholesterol, for they know of no other condition in which such low levels occur. The absence of beta-lipoprotein from the serum can then be confirmed by electrophoretic and immunochemical methods or by ultra-centrifugation.

To recognize the acanthocytes, it is essential to examine fresh undiluted blood when the typical spiky appearance of the majority of the red cells and their failure to form rouleaux will be obvious.

In February, 1960, Friedman, et al (6) described a case of profound hypocholesterolemia with clinical features which resembled all previously reported cases. They termed their report "Hypocholesterolemia in Idiopathic Steatorrhea." Subsequent examination of the peripheral blood in their patient revealed the presence of acanthocytosis.

In November of 1960, Mier, Schwartz, and Boshes (9) reported a case of "Acanthocytosis, Pigmentary Degeneration of the Retina, Ataxic Neuropathy: A Genetically Determined Syndrome with Associated Metabolic Disorder." Their patient was an 18-year-old Jewish boy who had suffered from celiac syndrome during childhood and subsequently developed a pigmentary degeneration of the retina, with progressive ataxic neuropathy. His red blood cells, like the other cases previously reported, showed the peculiar malformation described as acanthocytosis.

Laboratory studies in this boy demonstrated many biochemical abnormalities, including defective intestinal absorption of lipids, increased tolerance to carbohydrates, hypocholesterolemia, increased urinary excretion of copper, and elevation of certain enzymes in the serum.

From the neurological standpoint, with the exception of a few findings, all the cases reported, including that of Mier et al, possessed the common basic pathological picture indicative of a combination of posterior column and cerebellar components. On occasion, signs suggestive of pyramidal tract disease or peripheral nerve involvement were observed. The nature of these lesions probably accounted for the motor and sensory disturbances, the absent muscle-stretch reflexes, the inconsistent extensor-plantar responses, and the speech difficulties. The nystagmus was probably the consequence of brain stem involvement, rather than the manifestation of selective lesions of the vestibular apparatus or its nuclei. Certain of the complementary examinations performed in Mier's patient served to stress the fact that the process is not of a localizing nature. Nevertheless, the main manifestations, neurologically, were similar to those of the spinocerebellar degenerations. Furthermore, the age of onset, the presence of characteristic cerebellar and spinal cord symptoms, in combination with skeletal deformities of the feet (pes cavus) and the spine (kyphosis), brought this condition into the broad classical picture of Friedreich's ataxia.

They noted that, although a degenerative process of the retina is not a necessary component of any form of hereditary cerebellar degeneration, this association is occasionally observed, and when other elements are present, it becomes an integral part of a well-recognized familial syndrome, first described by Sigvald Refsum, under the name of "Heredopathia Atactica Polyneuritiformis." It is characterized by nystagmus, ataxia and other cerebellar signs, an atypical degeneration of the retina, and manifestations re-

sembling a peripheral polyneuropathy. The spinal fluid examination in most cases was normal. Occasionally, a striking elevation of protein is observed without an increase in the number of cells.

The resemblance between Refsum's syndrome and that reported by Mier, et al is of course remarkable from the clinical standpoint. However, certain laboratory determinations, such as the blood cholesterol, which was exceedingly low in Mier's patient, was within normal limits in those patients with Refsum's syndrome on whom they had been performed. Erythrocytic malformations have not been reported in Refsum's syndrome.

The ocular signs in the patients of Mier et al show some unusual features. On the initial ophthalmologic examination, which subsequently prompted the patient's first hospital admission, the changes observed were regarded as consistent with the diagnosis of retinitis punctata albescens. Later, slowly increasing deposits of dark pigment appeared and thus essentially changed the character of the retinal lesions. These were then considered as representative of the pigmentary degeneration of the retina. While closely related, the two conditions have several fundamental clinical differences. The former, originally described by the name of retinitis punctata albescens, is characterized by the presence in the fundus of numerous white dots. Pigmentary changes are absent, and the condition is stationary, or very slowly progressive. In some instances, it regresses, and the ophthalmoscopic findings may even disappear. Rarely, as in Mier's patient, pigmented deposits are found in association with the white dots, and the lesions become more rapidly progressive. Therefore, these findings illustrate Walsh's suggestion that retinitis punctata albescens represents a type of retinitis pigmentosa. Moreover, the evolutive changes support his proposal that, when cases in which pigment is not found are subjected to repeated examinations, development and increase in pigment occur in a great majority.

Certain aspects of the metabolism of carbohydrates, fats, and copper in Mier's patient diverge from the normal in many respects. The increased tolerance to glucose is striking, as demonstrated by the time required to return to normal or subnormal levels following the oral or intravenous administration of the test dose.

The metabolism of lipids also shows essential abnormalities. The blood carotene and vitamin A levels and absorption tests were highly suggestive of a deficient absorption of fats. To a certain extent, this finding was corroborated by the radioactive-tagged-fats test. The nonradioactive fat absorption test and the exceedingly low cholesterol further confirm the existence of an alteration of lipid metabolism. The lowered cholesterol is not necessarily the consequence of the impaired absorption of lipids, for endogenous synthesis of this substance is the primary factor affecting its concentration in the blood.

Probably of fundamental importance was the additional finding of a greatly increased urinary excretion of copper, which, in one instance, exceeded one milligram in 24 hours. Such an increased excretion, in the absence of proteinuria, had been considered specific for hepatolenticular degeneration pre-

vously. Although tremor on sustained movement may be the presenting symptom in certain cases of Wilson's disease, other clinical signs or laboratory findings suggestive of that entity were not apparent in Mier's patient. The Kayser-Fleischer ring, evidence of cirrhosis of the liver, and other signs of extrapyramidal involvement were lacking.

In 1930, Burr and Burr had indicated that fat-deficient rats seemed to possess "abnormal membranes." Since then, the idea that lipids, particularly essential fatty acids, have a structural function, has continuously gained support. It is obvious that the systems involved in Mier's patient were extremely dependent on these substances for structural and functional purposes. The surface of the erythrocytes is largely composed of lipids. When extracted and examined in the form of a suspension, the electrokinetic behaviour of these lipids has been shown to be similar to that of the intact erythrocyte. In deficiency of essential fatty acids, an increased fragility of erythrocytes is observed. The nervous system is also rich in unsaturated fatty acids. The experimental production of deficiencies is followed by changes which are closely related to the development of the nervous tissue. In the adult animal, little change is detected, but, in the young animal, the nerve cells receive their supply at the expense of other tissues. The specialized membrane formed by the Schwann cells in peripheral nerves is also rich in lipids and therefore dependent on these substances for its adequate structure and function.

Although in Mier's patient, there was an absence of consanguinity in the parents, they noted some instances of ataxic neuropathy and defective vision in the patient's family and suspected that these represented clinical variants of the complete syndrome.

They felt that this finding lent credence to Bassen and Kornzweig's report of the familial incidence of the disorder. They postulated that both parents were heterozygous and phenotypically normal, but capable of having homozygous descendants with the fully developed clinical syndrome. The available information then was highly suggestive of a recessive mode of inheritance.

In 1961, Schwartz, et al (19) had the opportunity to review the second patient reported by Bassen and Kornzweig in 1957, the brother of the original case, who was now 22 years old. They described a moderate progression of certain clinical findings and helped to consolidate the various phases of this unusual syndrome into a meaningful pathophysiologic pattern:

1. Retinitis pigmentosa. By 1961, the boy retained central vision only, with visual acuity of 20/50 and 20/40. The retinal degeneration was far advanced.

2. Neurological disorder. The ophthalmoplegia appeared to be developing insidiously despite the successful strabismus surgery at the age of 17. There was progressive, although slight, limitation in the field of action of all extraocular muscles and slight bilateral ptosis.

The weakness of the proximal limb muscles described in 1957 was now so severe that the boy could not stand without assistance and had great diffi-

culty turning in bed. There was weakness of the orbicularis oris and fibrillary movements were present in the tongue. The deep reflexes and plantar reflexes were absent. There was marked kyphoscoliosis. There was slight dysarthria compatible with cerebellar origin. There was severe impairment of position and vibratory sensation below the neck and slight impairment of cutaneous sensation in glove-and-stockings distribution.

There was a loud, precordial systolic murmur of the heart now present.

3. Acanthocytosis. When viewed in wet preparation or stained smears, roughly half of the erythrocytes appeared to have spines projecting from the surface. This appearance persisted if the cells were suspended in isotonic saline or normal serum.

4. Abnormal lipid metabolism. The serum concentrations of cholesterol, total lipid, triglycerides, phospholipids, and each of the individual phospholipid fractions were severely depressed. Vitamin A and carotenoids were not detectable in the serum. Beta-lipoprotein was not detected by immunoelectrophoresis, but there was some, although abnormally low, protein of this category as measured by ultra-centrifugation and paper electrophoresis. In the erythrocytes, there was marked decrease in linoleic acid concentration.

The gastrointestinal absorption of fat was markedly impaired; fatty acid absorption was also defective but this abnormality was less marked. Carotene was not absorbed at all, and vitamin A was absorbed to a limited extent but retained poorly.

These authors pointed out that the Bassen-Kornzweig syndrome is of importance because it is the first of the hereditary ataxias in which there is a clue to the metabolic abnormality. The fundamental defect appears to be a lack of beta-lipoprotein, the serum protein believed to be primarily responsible for the transport of phospholipids. The abnormality of myelin, retina, and erythrocytes might then be due to a deficiency of a similar lipoprotein in their membranes or could be secondary to a defective serum transport mechanism.

In April, 1963, Schwartz, et al (28), from the Neurological Institute of New York, had an opportunity to do further laboratory studies in the second case reported by Bassen and Kornzweig, i.e. the brother of the original case, and in addition, reported a new instance of the syndrome. With respect to the brother of the original Bassen-Kornzweig patient, the most striking abnormalities, from the laboratory standpoint, were those of lipid metabolism: There was defective fat absorption; reduction in levels of total serum lipids, triglycerides, cholesterol, and phospholipids, with all major phospholipids being involved; diminution of erythrocyte linoleic acid; and marked deficiency of low-density lipoproteins.

Their additional case was a 9½-year-old white boy, born of Italian parents who were fourth cousins. At the age of four months, he developed the celiac syndrome, which persisted up to the time of the report. At 6½ years, he began to have difficulty walking, fell frequently, and his gait became unsteady. These symptoms grew progressively worse, so that, by age 9½, he was

TABLE II
Summary of Clinical Data

Case No	Source	Age* (yr) and Sex	Parental Consanguinity	Ataxia	Retinal Manifestations	Intestinal Manifestations	Acantho- cytosis	Cardiac Manifestations
I	Bassen, Kornzweig [7]	18, F	First cousins	Yes	Retinitis pigmentosa	"Coeliac disease," improved later	Yes	
II	Singer et al [2], Jampel, Falls [4]	13, M	First cousins	Yes	Papillar degeneration	"Coeliac disease," improved	Yes	
III	Kornzweig, Bassen [3], Eder [13]	23, M	First cousins	Yes	Retinitis pigmentosa	"Coeliac disease"	Yes	Cardiac enlargement, systolic murmur
IV	Druetz [5], Lamv et al [13]	4, F	First cousins	Yes	Retinitis albenscent	"Chronic enteritis"	Yes	Abnormal electrocardiogram
V	Mier et al [8]	18, M		Yes	Retinitis pigmentosa	"Coeliac syndrome"	Yes	
VI	Friedman et al [6]	36, M		Yes	Bilateral lenticular opacities, myopic choroiditis	Steatorrhea	Yes	
VII	Salt et al [7]	15, F		No	No	"Coeliac syndrome"	Yes	
VIII	Lamv et al [70, 74]	6, M	Half brothers	Yes	No	Steatorrhea	Yes	
IX	Phillips [71]	7, F		No	No	Steatorrhea	Yes	
X	Mabry et al [9]	13, F		"Progressive neuropathy"	No	Steatorrhea	Yes	
Present case		31, F		Yes	Macular degeneration	Low unexplained prothrombin time, improved after vitamin K therapy	Yes	Cardiac enlargement and failure

* When first reported

(From Sobreville, Goodman, and Kane, *Am J Med*, 37(5):821, 1964.)

unable to walk unsupported. On physical examination, he appeared small and thin, with a stooped posture and seemed markedly underdeveloped and chronically ill. There was a mild degree of scoliosis, with right dorsal and left lumbar curvatures. There were bilateral equinovarus deformities of the feet, with marked limitation of passive dorsiflexion. There was generalized muscle weakness both proximally and distally. No fasciculations were seen. The deep reflexes were absent. A Babinski sign was constantly present on the right and intermittently on the left.

The gait was ataxic; he could not walk without assistance. There was marked impairment of finger-to-nose, finger-to-finger and heel-to-shin movements, with dysmetria. Vibratory sensation was absent below the neck, and position sense was grossly impaired in fingers and toes. There was a mild impairment of touch, pain, and temperature sensation in glove-and-stocking distribution.

There was bilateral ptosis, more marked on the right. There was marked lingual wasting and twitching.

Visual field examination was normal, without scotomata or constriction. The visual acuity, however, was only 20/50+1, O.S. and 20/50-1, O.D. There was no visible increase in choroidal pigment, and the optic discs were normal.

Laboratory studies showed the presence of acanthocytes, without other significant hematologic abnormalities. There was marked alteration in fat absorption and striking deficiencies of serum total lipids, triglycerides, cho-

TABLE III
Abnormalities of Lipid Metabolism

Serum:	Normal		Patient	
Cholesterol, Total	135-315	mgm. %	86-91	
Esters	70-78%		51	
Total Lipids	450-1000	mgm. %	285	
Neutral Fat	25-200	mgm. %	91	
Phospholipids	125-300	mgm. %	71	
Triglycerides	50-150	mgm. %	9	
Vitamin A	40-150	I. U./100 ml.	0	
Carotene	40-140	I. U./100 ml.	0	
<i>Serum Lipoproteins</i>				
Ultracentrifugation				
Beta-lipoprotein cholesterol (D < 1.063)	14.2		100-225	mgm. %
Alpha-lipoprotein cholesterol (D > 1.063)	58.7		40-75	mgm. %
Paper Electrophoresis				
Lipalbumin (% total protein)	36		12-24%	
Beta-lipoprotein (% total protein)	14		36-59%	
Immunoelectrophoresis	Absent		Present	
<i>*Phospholipids (MM %L)</i>				
	Plasma		Erythrocyte	
	Normal	Patient	Normal	Patient
Total lipid P	3.22	1.21	4.50	3.46
Cephalin	0.15	0.02	1.85	1.60
Lecithin	2.10	0.79	1.43	1.09
Sphingomyelin	0.59	0.33	1.01	0.73
Lyolecithin	0.24	0.04	0.08	0.06
<i>Gastrointestinal Absorption</i>				
	Peak of Absorption: % of Dose			
	Normal		Patient	
Fat— ¹³¹ I	11-19		2	
Fatty Acid— ¹³¹ I	5-9		4	
Glucose—Normal				
Xylose—Borderline				

* Data of Dr. G. B. Phillips.

(From Schwartz, et al, Trans Am Neurological Assoc., 1961.)

lesterol, phospholipids, erythrocyte linoleic acid, and serum low-density lipoproteins.

The case was considered then to be one of the Bassen-Kornzweig syndrome.

In their commentary, Schwartz, et al consolidate some of the knowledge extant as of 1963:

They note that neurological abnormalities were present in all but one of the patients reported, which at that time totalled eleven. In all patients, the first neurological symptom had been unsteadiness in walking. The combination of cerebellar signs (ataxia of gait, trunk, and extremities, with titubation and dysarthria), severe proprioceptive deficit, and the Babinski sign, especially in combination with kyphoscoliosis, is similar to Friedreich's ataxia. The clinical neurologic findings imply degeneration of posterior and lateral columns of the spinal cord and spinocerebellar pathways. In addition, sensory abnormalities indicated that peripheral nerves are involved.

The muscular weakness presented some difficulty in their analysis. The severe wasting and twitching of the tongue in the case of Schwartz et al suggested that the weakness might be neural in origin, but they concede the possibility that the limb and trunk weakness may be in part due to a myopathy. The ophthalmoparesis is again somewhat uncertain; the pupils were normal, and ophthalmoplegia in other hereditary ataxias may be myopathic in origin.

With respect to the retinal disorder, they note that pigmentary changes in the retina occurred in six of the eleven cases, and, in one additional case, electroretinography was abnormal despite the normal appearance on fundoscopic examination. The patient reported by Singer et al had no retinal disease at age 13, but, at age 19, retinitis was marked. Therefore, the four patients without retinal lesions, all under 13 years of age, were still considered to be at risk.

The retinal changes have been variously described as "atypical retinitis pigmentosa with macular involvement," "typical retinitis pigmentosa," "retinitis punctata albescentis with retinal pigmentary degeneration" and "myopic choroiditis." Ring scotomata and contracted visual fields have been common to all, and the pigmentary changes have been progressive.

With respect to the hematologic disorder, acanthocytosis has been present in all patients, and this is the most easily identified abnormality. The low erythrocyte sedimentation rate and absence of rouleaux formation have been constant. Studies on interconversions of acanthocytes and normal erythrocytes by Switzer and Eder have shown that acanthocytes can be converted to normal erythrocytes by the addition of small amounts of oleyl ethers or esters of non-ionic detergents, such as polysorbate 80 (Tween 80).

As for the lipid disorders, several aspects of lipid metabolism are abnormal: 1. There is a deficiency in the serum low-density lipoproteins. 2. The relative proportion of serum and red cell lipids is abnormal. 3. There is impairment of intestinal absorption of fat. Schwartz, et al confirmed the low concentrations of serum cholesterol noted by previous workers and emphasized the discovery of Salt, et al in ascribing to the marked deficiency of beta-lipoproteins the specific metabolic defect in these patients. There is a deficiency of the low-density lipoproteins (D 1.019–1.063) and of a very low density lipoprotein (D less than 1.019). The lipoproteins of the first category may be completely absent, as in the Bassen-Kornzweig boy. As a consequence of decrease in low-density lipoproteins, the serum cholesterol and phospholipids are markedly reduced. Of the eleven cases reported, serum cholesterol concentrations varied between 30 and 86 mg/100 ml.

The reduction of plasma phospholipids affects the three major individual phospholipids, viz., lecithin, sphingomyelin, and cephalin. The absolute concentration of all phospholipids has been reduced in all patients studied. The relative concentration of lecithin has been decreased, and the relative concentration of sphingomyelin increased.

Analysis of erythrocyte fatty acids by gas chromatography was undertaken in five patients. The only significant abnormality was a reduction in linoleic

acid in all five. Ways et al showed that the percentage of linoleic acid in individual phospholipid fractions was diminished in both acanthocytes and cells of normal appearance. Because the lecithin fraction normally contains about 75 percent of all the linoleic acids found in erythrocyte phospholipids, they suggested that the alteration in relative concentrations of the individual phospholipids might be directly related to the reduction in linoleic acid. Steatorrhea, or fatty diarrhea, was always the initial symptom and was present in all cases with onset between six weeks and two years. Intestinal absorption of I^{131} -labeled-fat and fatty acids was studied in seven patients and was markedly impaired in all. Stool fat was increased in nine cases. Vitamin A and carotene absorption tests in all six patients tested were markedly defective. The duodenal or jejunal mucosa was examined histologically in five cases; all showed slightly irregular villi, with the columnar cells of the mucosa having an unusually pale cytoplasm which appeared to be vacuolated. These findings were unlike those of uncomplicated celiac disease.

Although it was, by this time, generally felt that the inability of the body to form the beta-lipoprotein molecule in these patients was fundamental to the defect in the Bassen-Kornzweig syndrome, it was noted too that infusion of beta-lipoprotein failed to correct the defect in lipid absorption.

Schwartz, et al pointed out, with regard to pathogenesis, that the disorder seems to involve at least four lipid membranes: the erythrocytes, the pigment layer and ganglion cells of the retina, the small intestine, and myelin. Within the nervous system, the disorder seems to be selective in causing tract degeneration, rather than involving all myelin or being a diffuse neuronal disorder.

They note that, although the impaired absorption of lipids might be the cause of diminished concentration of the very low-density lipoproteins, such striking reductions in the low-density lipoproteins and the neurological and retinal abnormalities in this syndrome do not occur in other forms of steatorrhea. The extremely low serum lipid values are below those which have been obtained after prolonged lipid deprivation.

They attempt to explain all the findings on the basis of a single genetically determined protein deficiency, in this case the low-density lipoprotein (beta-lipoprotein). After immunoelectrophoretic analyses, they concluded that the protein is therefore actually deficient and has not merely lost its functional lipid-binding activities.

How the deficiency of beta-lipoprotein causes the Bassen-Kornzweig syndrome clinically is not altogether clear. Two possibilities have been suggested: 1. Beta-lipoprotein normally contains about 75% of total circulating lipids, and the deficiency might result in the failure of transport of essential lipids to the affected tissues. This would not account for the absorptive defect since beta-lipoprotein is not known to play a role in absorption. 2. It is possible the lipid membranes of various tissues normally contain a protein similar to beta-lipoprotein of serum and that the tissue lipoprotein is also affected in the disease.

As to treatment, they suggest that the celiac syndrome is diminished by a

low-fat diet but not alleviated by the gluten-free diet. Adrenal steroids were tried in four cases with no definite benefit. DiGeorge et al administered a cottonseed oil emulsion intravenously for 39 consecutive days. They reported "marked clinical improvement and conversion of acanthocytes to normal cells, but there was no change in the level of beta-lipoprotein, and therapy had to be discontinued because of side-effects."

In August, 1963, Sobrevilla, Goodman, and Kane (31) in Boston reported a case of the Bassen-Kornzweig syndrome embodying the main features of the condition but with additional cardiac disturbances of a severe character which precipitated the patient's death. The dominant picture in this patient was the neurologic syndrome which prompted medical therapy at the age of fifteen. Historically, however, gait disturbances went back to early childhood. The neurological alterations included ataxia, deep tendon areflexia, hypotonia and loss of vibratory sense, with wasting of the leg muscles and deformities of the feet. These stationary symptoms of atypical spinocerebellar degeneration prompted the diagnosis of the Roussy-Levy syndrome.

The visual disturbances began at thirty years of age, with "blurred vision," diagnosed as due to right macular hemorrhage and left macular degeneration. The signs and symptoms of visual involvement continued to progress, with fundal hemorrhages. On the last admission, the visual acuity was greatly diminished; brown pigment deposits were present at both maculae.

The erythrocytes in this case had the typical morphology of acanthocytes and were first observed in the patient at the age of thirty. The osmotic fragility before and after incubation was abnormally increased. The review of the previous blood smears showed the red cell abnormality to be present in all of them. Hyperglycemia, glycosuria, and a low serum cholesterol level were present, with serum proteins of 6 gm%.

This patient did not have steatorrhea or celiac disease; however, the presence of an abnormal prothrombin time, which did respond to vitamin K therapy, suggested abnormalities of absorption.

Terminally, the patient was admitted with severe cardiac decompensation, cardiomegaly, tachycardia, gallop rhythm, and orthopnea. She had a high venous pressure and prolonged circulation time. She had been digitalized and, after admission, presented symptoms and signs of digitalis intoxication, followed by arrhythmias, hypotension, and finally cardiac arrest.

The autopsy findings revealed demyelinating lesions of the anterior column, spinocerebellar tracts, and loss of nuclei in the anterior horns and cerebellar molecular layer, with loss of Betz cells. The marked optic atrophy and macular changes accounted for the visual disturbances. The cause of these lesions was not precisely known, but hereditary predilection was well established. The relationship of these lesions to the low beta-lipoprotein value and red cell acanthocytosis was again well documented but not fully explained. A moderate erythroid hyperplasia of the bone marrow was found at autopsy.

Sobrevilla et al note that the sedimentation rate is low in Bassen-Kornzweig syndrome because of the prevention of rouleaux formation by the acanthocytes.

Estimation of the serum proteins of the present patient showed a reduction in all the fractions of the globulins, more markedly the beta and gamma fractions.

The similarity to spinocerebellar ataxia of the Friedreich form is striking. Guillain and Molaret were first to note cardiac disturbances associated with Friedreich's ataxia. A review of the incidence of cardiac disturbances in Friedreich's ataxia reveals that 55 percent of the patients exhibited major cardiac abnormalities. Russell proposed that "the cardiac and neurological manifestations probably arise from an error in a genetically determined biochemical process important to the functional and structural integrity of both the nervous system and the heart."

In February 1965, Becroft, Costello, and Scott (32) from the Princess Mary Hospital and Auckland Hospital of Auckland, New Zealand, reported a 17-month-old Maori child with Bassen-Kornzweig syndrome. In addition to acanthocytosis, α -beta-lipoproteinemia, hypocholesterolemia, and steatorrhea, he had incipient neuropathy. The child also had impairment of renal function, aminoaciduria, and suffered from recurrent pulmonary infections. Their case was diagnosed at the age of ten months, and, because of the unusual features, died at age one and one-half years.

At age ten months, the Maori child appeared mentally retarded, weighed 11 lbs, 5 oz (5.2 kg). His head appeared small, and the occiput was flattened; slight flexion contractures of the knees were present. The deep reflexes were diminished in the legs; signs of bronchopneumonia, with bronchospasm, were present. There was no evidence of retinopathy. Laboratory investigations disclosed classical acanthocytosis, virtual absence of serum beta-lipoproteins, profound hypocholesterolemia, considerable reduction of serum fatty acid esters and serum carotenoids. Steatorrhea was present. These investigations confirmed the clinical impression that the child was suffering from the Kornzweig-Bassen syndrome.

Further investigation revealed a persistently elevated blood urea. A generalized aminoaciduria was present, but the serum amino acids were normal, indicating that the aminoaciduria was of a low-renal threshold type.

During his stay in the hospital at that time, the child had several episodes of asthma, which responded satisfactorily to treatment; no dietary treatment, such as fat restriction, was attempted, but vitamin supplements were given.

At the age of 17 months, he was readmitted to the hospital for reappraisal of renal function. At that time he was suffering from otorrhea and basal bronchitis for which he received antibiotics. There was still no evidence of retinopathy. Blood urea was 40 mg/100 ml. Urine bacterial count was 10,000/ml.

Three weeks after admission to the hospital, he suffered an exacerbation of bronchitis and asthma, which was associated with cardiac enlargement and left ventricular failure. He responded initially to digoxin but deteriorated again and died on the seventh day of the illness.

In their discussion of the case, Becroft et al observed that the low serum cholesterol level fell within the range of 20 to 50 mg per 100 ml previously re-

ported with the Bassen-Kornzweig syndrome. Ultracentrifugal analysis of the patient's serum, using a density-gradient method, showed that the small amount of cholesterol present was associated with the high-density lipoprotein (alpha-lipoprotein). This analysis showed no detectable low-density lipoprotein (that is, beta-lipoprotein), and no chylomicra were present. The lipoprotein pattern was similar to that reported by Schwartz, et al (1963) and Salt et al (1960). The density-gradient used was identical to that employed by Dr. K. W. Walton in investigations on the case reported by Salt and his colleagues. Immunoelectrophoresis also failed to reveal any detectable beta-lipoprotein in their patient's serum.

They note that, in normal people, seventy percent of plasma cholesterol, fifty percent of phospholipids, and virtually all of the plasma carotenoids are carried by the beta-lipoproteins. The immunological studies showing virtual absence of the protein components of beta-lipoprotein in their patient are compatible with the hypothesis that one of the major defects was complete absence of this normal transport system.

In young children without the ocular and neurological manifestations of the Bassen-Kornzweig syndrome, recognition of acanthocytes in blood films is the most likely means by which the diagnosis can be reached. In their patient, the red cells were recognized as abnormal in infancy but had to be carefully differentiated from "Burr cells," "pyknoocytes" and "microspherocytes." In acanthocytosis, the cells comprise one-third to one-half of all cells and will be accompanied by many showing normal crenations. In the "burr" cell phenomenon, only a small proportion of abnormal cells will have this appearance; the remainder will show a wide variety of irregular shapes, among which triangular, crescentic, and helmet-shaped cells will be prominent. In "pyknoctosis," it has been stated that one-third to one-half of the cells will resemble the acanthocytes, but there will be few if any other abnormal cell types.

Acanthocytes retain their abnormal shape when incubated in normal serum. Conversely, the serum of patients with this disorder does not convert normal cells into acanthocytes. The abnormality would therefore appear to be inherent in the erythrocyte rather than in the serum. It had been shown that acanthocytes can be converted into the shape of normal erythrocytes by exposure in vitro to a non-ionic detergent (Switzer and Eder, 1962) and in vivo by administration of cottonseed oil emulsion intravenously (DiGeorge, Mabry, and Auerbach, 1961).

Then, too, other constant hematological features in acanthocytosis are absence of rouleaux formation and a low erythrocyte sedimentation rate. The case of Beeroft et al had an erythrocyte sedimentation rate of 3 mm (Westergren) at the height of a respiratory infection. Anemia is not a constant feature in this disorder. The anemia in Beeroft's patient appeared to respond to intramuscular iron and folic acid and was presumably nutritional in origin.

A final puzzling feature in their case was the development of cardiac failure with pulmonary edema during the terminal episode of bronchitis and asthma. This complication contributed to his death. Schwartz, et al (19) in

1961 mentioned the presence of cardiopathy. Their diagnosis of cardiomyopathy was based on the presence of a loud systolic murmur. Whether cardiomyopathy can occur as a complication of the Bassen-Kornzweig syndrome will become apparent only as a greater number of cases are recognized and studied. Cardiomyopathy has been reported in other malabsorption states (McGIVEN, 1962).

Beerof et al favor the general view that the disease is due to an autosomal recessive gene. They accept the familial occurrence (Kornzweig-Bassen, 1957) and frequency of parental consanguinity as evidence in this direction. They agree with Salt et al who favored Singer's original view that the ocular and nervous disturbances were genetically determined and agreed that a factor essential for the production of beta-lipoprotein was also essential for the normal structure and function of nerve cells. However, they did not dismiss the possibility that these disturbances result from abnormal fat absorption and transport.

Also in February, 1965, Forsyth, Lloyd, and Fosbrooke (33) from England reported the instance of a 7-year-old boy with diarrhea in early infancy who was found to have a-beta-lipoproteinemia. The typical features of the syndrome, that is, steatorrhea, acanthocytosis, retinal degenerative changes, and an ataxic neuropathy were all present. He was also mentally retarded, a finding reported in three other patients with the condition. His parents' marriage was consanguineous.

In their discussion of the pathogenesis of the various features of the syndrome, they agree with the concepts of other writers in imputing to the prolonged absence of beta-lipoprotein from the serum a causative role in the changes found in the erythrocytes, retina, central nervous system, and intestinal tract. They assert that a low fat diet has been successful in relieving the intestinal symptoms and in improving growth and development of their patient.

In 1966, an interesting report from Holland appeared by Van Buchem, et al (34) in which they call attention to cases of the Bassen-Kornzweig syndrome where only part of the classical clinical manifestations are present. Their first case was a 46-year-old man who was entirely symptom-free found to have a remarkably low serum cholesterol level (70-80 mg%) during a mass screening program. Nine years earlier, the patient had been treated for lymph node swellings in the neck and axillae. After extensive laboratory testing, it was noted on paper electrophoresis that there was a marked reduction of the beta-lipoproteins. A chest x-ray revealed extensive fibrosis in both upper lung fields with prominent hilar markings. The plasma of this patient was found to have a markedly reduced content of total lipids, cholesterol, cholesterol esters, phospholipids, and especially triglycerides. The lecithin-sphingomyelin ratio was decreased. The linoleic acid content and the arachidonic acid content of the cholesterol esters, the triglycerides, and the phospholipids were markedly reduced, but, proportionately, the greatest reduction was in the cholesterol esters and triglycerides.

This first patient then had, in addition to the biochemical phenomena of beta-lipoprotein deficiency, a compensated increased hemolysis with shortened life-span of the erythrocytes, as found in only a few patients with the Bassen-Kornzweig syndrome. Remarkably enough, in this patient, the reaction to the direct Coombs' test was positive with anti-gamma-globulin serum, a reaction always found to be negative in other similar patients.

Van Buchem, et al had the opportunity to examine some of the relatives of this patient. The brothers, 38 and 39 years old respectively, also had a decreased beta-lipoprotein content of the serum but to a lesser degree than the original patient. With immunoelectrophoresis and immunodiffusion, the serum of the first brother reacted with a 1:8 dilution, where the serum of three normal men of the same age group reacted at a dilution of 1:32. The brothers had no physical abnormalities in particular; there were no neurological disturbances and no involvement of the fundus oculi and no acanthoeytosis. However, in the two brothers, the plasma cholesterol, phospholipids, and, especially, triglycerides were reduced. Corresponding with the reduction in the lipids, the linoleic acid content was also decreased.

Their comments are of interest because they call attention to the several degrees of beta-lipoprotein deficiency. Their first patient showed a marked deficit of beta-lipoprotein with the same change in the lipid pattern of the plasma and erythrocytes that occurs in the classic Bassen-Kornzweig syndrome. However, the characteristic clinical manifestations of steatorrhea and neuropathy, acanthoeytosis, and atypical retinitis pigmentosa were not present. Isselbacher et al proved that in the classic cases with steatorrhea, fatty acids and diglycerides are taken up by the intestinal mucosa and converted into triglycerides. These investigators believed that there was either a disturbance in the formation of chylomicrons in the intestinal mucosa or a disturbed release of chylomicrons in the lymph vessels. Due to this blockade in the removal of triglycerides, the fat accumulates in the intestinal mucosa, becoming manifest in the accumulation in the epithelial cells. This might lead to the steatorrhea. Their concept is consistent with the fact that in the first case of Van Buchem et al with no steatorrhea, no fat accumulation in the jejunal mucosa was observed. There was apparently sufficient beta-lipoprotein for removal of the fat. This explains too why the patient's brothers who had only mild beta-lipoprotein deficiency did not suffer from steatorrhea. Van Buchem's patient did not show the decreased lactase activity of the jejunum observed by Isselbacher et al. The fatty liver found by Isselbacher would also be the result of the disturbed removal of the triglycerides. Liver fat consists mainly of triglycerides and cholesterol esters. Van Buchem's patient showed a mild steatosis of the liver which might be explained by the insufficient synthesis of pre-beta-lipoprotein. Van Buchem et al believed the evidence is impressive that the primary disturbance is a deficiency of beta-lipoprotein. That this is really a deficiency of beta-lipoprotein and not inability of the protein to bind fat is shown by immunoelectrophoresis.

The deficiency of the lipids in the plasma is understandable since, normally, beta-lipoprotein contains about 75 percent of the total circulating lipids.

Isselbacher et al believed that the low linoleic acid content was caused by disturbed absorption. In Van Buchem's patient, who also showed this marked decrease in linoleic acid content, there was no disturbance in the absorption of the fat, xylose, and glucose. They, therefore, instituted a four weeks' diet containing a fat of which 50 percent of the fatty acids was linoleic acid. The serum and erythrocyte lipids were determined before and two and four weeks after beginning the diet. Analysis of the fatty acid composition of the lipids demonstrated the marked influence of the diet rich in linoleic acid. The linoleic acid content of the phospholipids, the cholesterol esters, and, especially the triglycerides increased strikingly, whereas the oleic acid content in all these fractions decreased. The fatty acid pattern changed markedly under the influence of the diet: the stearic acid and oleic acid content decreased significantly and the linoleic acid and arachidonic acid contents increased.

These results were felt to indicate that the intestinal mucosa of their patient was indeed able to absorb linoleic acid, in view of the sharp increase in the linoleic acid content of the erythrocytes, the serum triglycerides, and cholesterol esters when sufficient linoleic acid was present in the diet. Why the linoleic acid content is reduced in these patients and why there is a shift in the lecithin-sphingomyelin ratio in plasma and erythrocytes remains unknown. Linoleic acid deficiency in itself does not cause a decrease in the lecithin-sphingomyelin ratio of plasma and red blood cells.

Van Buchem et al note that therapy directed at the cause is, of course, impossible. To cure the possible steatorrhea, a low fat diet has proved to be the best method; it is followed by considerable improvement in the general condition. Isselbacher et al began with the premise that fatty acids with chain lengths less than C-12 are normally not esterified in the intestinal mucosa and reach the liver via the portal vein as nonesterified fatty acids bound to albumin. Therefore, they gave their patient a diet with 80% octanoate (C-8) and 2% decanoate (C-10). With 30 to 45 grams of these medium-chain triglycerides, the patient soon gained weight, and the loss of fat in the stools decreased from 20 to 8%. After eight months, the general condition had improved, and muscular strength increased, but the neurologic disturbances remained unchanged.

The observations of Van Buchem et al of beta-lipoprotein deficiency in three brothers correspond with the observations of Kuo and Basset who found it in one male and two female members of a family and those of Salt and co-workers (10) who found beta-lipoprotein deficiency in the two parents of the young patient who had the classic Bassen-Kornzweig syndrome. These data make it probable that an autosomal recessive gene with variable penetrants is involved in this hereditary disease.

Since it has become clear that many degrees of beta-lipoprotein deficiency exist, even in subjects who are entirely symptom-free, it is probable that this deficiency does not occur as rarely as has been supposed. Only if traces of beta-lipoprotein are present, or if it is entirely absent, do steatorrhea, neuromuscular disturbances, acanthocytosis, and retinal changes develop. A slighter degree of beta-lipoprotein deficiency may, however, be associated

also with the characteristic lipid pattern of the plasma and red blood cells, and, the greater the deficiency, the more characteristic the pattern.

If there is no beta-lipoprotein present or only traces of it, the full-blown Bassen-Kornzweig syndrome develops. A constant feature of this syndrome is disturbed fat absorption, with accumulation of fat in the epithelium of the intestinal mucosa, and acanthocytosis; ultimately, neuropathy and, usually, disturbances of the ocular fundus resembling retinitis pigmentosa develop.

If there is still about ten to twenty percent of beta-lipoprotein present, steatorrhea, fat accumulation in the epithelium of the intestinal mucosa, neurological disturbances, and acanthocytosis are absent. The changes in the lipids and fatty acid patterns in plasma and red blood cells, however, are the same as those present in the absence of beta-lipoprotein.

Van Buchem et al reiterate that, after consumption of food containing much linoleic acid, the linoleic acid content of the erythrocytes, as well as the serum cholesterol esters, phospholipids, and triglycerides increase considerably.

Beta-lipoprotein deficiency is an hereditary disease; probably an autosomal recessive gene is involved.

Summary and Conclusions

The description in 1950 by the original authors of the Bassen-Kornzweig syndrome entailed the basic elements of: 1. A neuromuscular disorder resembling Friedreich's ataxia. 2. A retinitis pigmentosa-like condition of the eyes. 3. Acanthocytosis. 4. Steatorrhea.

From the outset, there was insight into the hereditary nature of the condition and its relation to and dependence upon consanguinity. Then, in 1952, Singer and his group reported a remarkably similar case and gave the descriptive term of "acanthocyte" to the abnormal red cells. In 1957, Kornzweig and Bassen reported on the brother of their original case, carefully delineating the progression of the syndrome over the intervening seven-year period.

In 1958, Jampel and Falls, in addition to reporting an extremely interesting follow-up of the patient of Singer, Fisher, and Perlstein, drew attention to the phenomenally low blood cholesterol level of 37 mg%, which was characteristic of the condition. Another case of acanthocytosis was described by Druez, who contracted the designation to "acanthocytosis" in 1959.

It was in 1960 that Salt and his group, besides reporting an additional case of the clinical syndrome, called attention to the fundamental role of the deficiency in beta-lipoprotein. Their investigation of the defective fat absorption and transport made it possible for them to enlarge the previous concept of the syndrome. They considered a-beta-lipoproteinemia to be an in-born error of metabolism with a recessive mode of inheritance. The primary gene effect appeared to be an inability to form the beta-lipoprotein molecule and was probably concerned with the protein moiety. Correspondingly, cholesterol and the phospholipids of the serum were markedly reduced. They emphasized that the diagnosis of a-beta-lipoproteinemia should be suspected in a patient with steatorrhea associated with a very low serum cholesterol.

In 1960, Mier and his group, in addition to reporting another case with the syndrome, further elaborated the many biochemical abnormalities of the condition, including defective intestinal absorption of lipids, increased tolerance to carbohydrates and a peculiar increase in the urinary excretion of copper, as well as the elevation of certain enzymes in the serum. Meanwhile, the concept that lipids, particularly essential fatty acids, have a structural function, had continuously gained support. The systems involved in Mier's patient and in the Bassen-Kornzweig syndrome generally were extremely dependent on these substances for both structural and functional purposes. It became clear that the surface of the erythrocytes was largely composed of lipids, and that nervous tissue, both in the brain and spinal cord and in the retina of the eye, were likewise rich in unsaturated fatty acids. The specialized membrane formed by the Schwann cells of peripheral nerves was also rich in lipids and therefore dependent on these substances for adequate structure and function. In this way, the profound disturbances in the multiple organ systems concerned in the Bassen-Kornzweig syndrome were gradually brought together into a meaningful pathophysiological pattern which could be best explained on the basis of a fundamental deficiency in the all important beta-lipoprotein.

In 1961, Schwartz and his group had the opportunity to review the second patient reported by Bassen and Kornzweig, and, in addition to consolidating the various phases of the syndrome, pointed out that the Bassen-Kornzweig syndrome is of more than ordinary importance because it is the first of the hereditary ataxias in which a clue existed as to the metabolic abnormality. By 1963, Schwartz and his group, after further laboratory studies of the second Bassen-Kornzweig case, delineated the abnormalities in lipid metabolism and called attention to the important diagnostic point that acanthocytosis had been present in all instances of the syndrome and that this was the most easily identified abnormality. The low erythrocyte sedimentation rate and absence of rouleaux formation tended to be constant findings.

In 1963, Sobrevilla and his group reported a case of the Bassen-Kornzweig syndrome embodying the main features of the condition but with additional cardiac disturbances of a severe character which precipitated the patient's death. As a result, autopsy findings became available for the first time, revealing demyelinating lesions of the anterior column, spinocerebellar tracts, and loss of nuclei in the anterior horns and cerebellar molecular layer with loss of Betz cells. A moderate erythroid hyperplasia of the bone marrow was found, as well as marked optic atrophy and macular changes in the eye.

In 1965, Beeroft and his group reported an incidence of the Bassen-Kornzweig syndrome in a 17-month-old Maori child from Auckland, New Zealand. The child had all of the clinical and laboratory findings of the Bassen-Kornzweig syndrome and demonstrated that the condition is not in any sense peculiar to a geographic area or an ethnic group.

Then, in 1966, the interesting report from Holland of Van Buchem and his group drew attention to cases of the Bassen-Kornzweig syndrome where only part of the classical clinical manifestations are present. From the standpoint of therapy, they stressed the desirability of a low-fat diet, which, at the very

least, reduces the steatorrhea and improves the nutritional status of the patient. Along with Isselbacher et al, they pursued the theory that medium-chain triglycerides are not normally esterified in the intestinal mucosa and can therefore be better assimilated by these patients. Experience has shown that such a diet does indeed tend to improve their general condition, but the specific neurologic disturbances remain unchanged.

It has thus become clear that many degrees of beta-lipoprotein deficiency exist, even in subjects who are entirely symptom-free; thus, it is probable that the deficiency is not quite so rare as has been supposed. Only if traces of beta-lipoprotein are present or if it is entirely absent do steatorrhea, neuromuscular disturbances, acanthocytosis, and retinal changes develop, that is, the full-blown Bassen-Kornzweig syndrome. A slighter degree of beta-lipoprotein deficiency may, however, be associated also with the characteristic lipid pattern of the plasma and red blood cells, and, the greater the deficiency, the more characteristic the pattern.

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Bilateral Complete Internal Carotid Artery Occlusions in a Patient with Transient Neurologic Deficits

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The increased use of angiography in the diagnosis of cerebral disease has led to the occasional discovery of unanticipated severe, unusual, or multiple lesions of the cerebral circulation. The patient reported here, presenting with transient neurologic deficits, had complete occlusions of both internal carotid arteries. The majority of such patients survive for only short periods of time or have severe neurologic deficits (1-10). This patient represents the small group who, despite the severity of their lesions, show only mild neurologic deficits (4, 6-8, 11, 12).

Case Report

A 65-year-old woman was hospitalized on April 24, 1967, with somnolence, confusion, dysphasia, and motor seizures. Twelve years previously she had the acute onset of mental and communication deficits and defects in motor and sensory function on the right side. She improved rapidly and was discharged three weeks later with slight right-sided weakness and speech limited to simple sentences. Four months later her only deficits were a hesitancy in initiating speech, word-finding difficulty, and a mild paresis on the right. She functioned well as a housewife during the ensuing 11 years until several hours prior to the admission in April 1967 when she became somnolent, slow of speech, confused, and dysphasic. She had three generalized seizures with movements which began on the right side of the face and spread to the arms and legs, each lasting ten minutes. Following the first seizure, there was constant twitching of the right side of the face for the next few hours. At the time of admission there were episodes of rhythmic, clonic twitching, starting on both sides of the forehead and eyelids and spreading to the right side of the mouth, tongue, palate, and uvula. The episodes of twitching, lasting 60 to 90 seconds, recurred every 2 to 3 minutes; she remained conscious and looked about during the episodes.

When tested on multiple trails, mental deficits included: (a) disorientation for calendar date, day of week, time of day and place, (b) errors in simple calculations and reversals of three and four letter words, (c) poor performance on commands, especially those of crossing the midline, and (d) bilaterally positive face-hand responses. She used words incorrectly, her sentence structure was awkward, and her speech was erratic with a bursting quality. The right-sided extremities were weak with greatest deficit in the hand which moved poorly in coordinated motions. Pain, temperature, and vibratory sensibilities were decreased on the right side; a Babinski sign was present on the right. The remainder of the neurological examination was normal.

The carotid pulses were not palpable above the level of the thyroid cartilage. There were systolic bruits with thrills present in both carotid arteries below the level of the thyroid cartilage; a soft systolic murmur was heard at the base of the heart. The blood pressure was 220/85. The remainder of the physical examination was normal. Compression of each carotid artery for five seconds induced no new signs. Ophthalmodynamometer readings in each eye were normal. Intravenous injection of 350 mg Amobarbital (Amytal®) induced marked aphasia and increased the right-sided weakness.

The lumbar puncture on admission showed slightly xanthochromic fluid; two days later

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this had cleared. Opening pressure was 80 mm. The cerebrospinal fluid protein was 33 mg%, sugar was 133 mg%. The electroencephalogram on admission showed a large amount of polyspike sharp waves and single spikes in the left frontal and temporal leads and bursts and runs of 1.25-3 cps up to 150 microvolts in frontal and anterior temporal regions on the left side. Repeat electroencephalogram the day of discharge showed some increase in the abnormality with bursts of 1.5-4 cps up to 150 microvolts and 5-7 cps up to 70 microvolts in the frontal and temporal regions. This activity was noted mostly on the left, but occasionally on the right side. Triphasic sharp waves occurred independently on the left and right. The skull x-rays, brain scan, and routine laboratory studies were normal.

The Neuroradiologic Examination

The left carotid angiogram disclosed complete occlusion of the left internal carotid artery (Fig 1, arrow). The needle tip is seen in the common carotid artery slightly below the bifurcation. Narrowing is present at the origin of the left external carotid artery. The right carotid angiogram disclosed complete occlusion of the right internal carotid artery (Fig 2, black arrow). The needle tip is seen in the common carotid artery below the bifurcation. There is marked narrowing at the origin of the right external carotid artery (white arrow). A right brachial angiogram (Fig 3) demonstrated the enlarged right vertebral, basilar, and posterior communicating arteries. The right vertebral artery is enlarged to the greatest degree and is approximately the size of a normal common carotid artery. At the circle of Willis the enlarged posterior communicating arteries fill both the anterior and middle cerebral arteries, thus supplying the anterior cerebrum with its circulation. The vertebrobasilar circulation supplies the entire cerebral circulation; there is no collateral circulation between the internal and external carotid systems. The lateral view (Fig 4) demonstrates the anterior cerebral circulation filling bilaterally through the posterior communicating arteries. Again, there is no evidence of collateral circulation between the internal and external carotid arterial systems.

An aortic arch study via a catheter introduced into the left femoral artery and threaded to the aortic arch showed the origins of the innominate, both common carotids, the vertebrals and the subclavian arteries to be normal.

Hospital Course

The facial twitching stopped after the intravenous injection of 15 mg Diazepam (Valium®). Twitching recurred 2 and 18 hours later. It was less severe, and was stopped abruptly each time after the intravenous injection of 5 mg of Diazepam. Facial twitching recurred 24 hours after admission, lasted ninety minutes, and stopped slowly. In general, the clinical status improved rapidly. Within the first 24 hours the strength in the right arm and leg improved to the preadmission status and did not change thereafter. By the tenth hospital day the patient's speech and mental function had reached the preadmission level. One month after discharge the only deficits were: stumbling over words, mild dysnomia, and mild dystaxia on the right.

Discussion

The severity of symptoms following occlusions of major vessels to the brain is determined by the nature and quantity of collateral circulation that can be established and the time it takes for the complete occlusion to occur (4, 13). Three of five monkeys recovered completely after sudden complete occlusion of both carotid and vertebral arteries for thirty minutes (14). Similar results were reported by Cooper (15), Andreyev (16), and Gardner (17). Djemann (10) reported the only case of acute bilateral carotid occlusion in a human; the patient died rapidly with loss of brainstem function.



FIG. 1. Left carotid angiogram demonstrating complete occlusion of the left internal carotid artery (arrow). Lateral view.

The patient reported here had collateral circulation sufficient to sustain life with moderate neurologic deficit. It is probable that both carotid occlusions were of long-standing duration. The character of the collateral circulation bears this out since the posterior circulation could not have made so striking a compensatory enlargement in a short period of time. How slowly the collateral enlargements occurred or whether the carotid occlusions were present developmentally or in early life cannot be ascertained. The character of certain collateral channels have been interpreted as implicating congenital carotid occlusions (18, 19). However, there is no general agreement that such collateral patterns are features exclusively of congenital occlusions.



FIG. 2. Right carotid angiogram demonstrating complete occlusion of the right internal carotid artery (dark arrow) and stenosis of the right external carotid artery (white arrow).

In patients with unilateral carotid artery occlusions, the collateral circulation was most often via the external carotid arteries to the ophthalmic or meningeal arteries. Mount and Taveras (20) found collateral circulation via (a) the circle of Willis, (b) the meningeal branches of the anterior, middle, and posterior cerebral arteries, (c) the external carotid artery via the ophthalmic artery and its branches with the internal and external maxillary and superior temporal arteries, (d) the middle meningeal artery and the meningeal branch of the internal carotid artery, and (e) unnamed arteries passing through the dura and anastomosing with vessels on the surface of the brain. Other

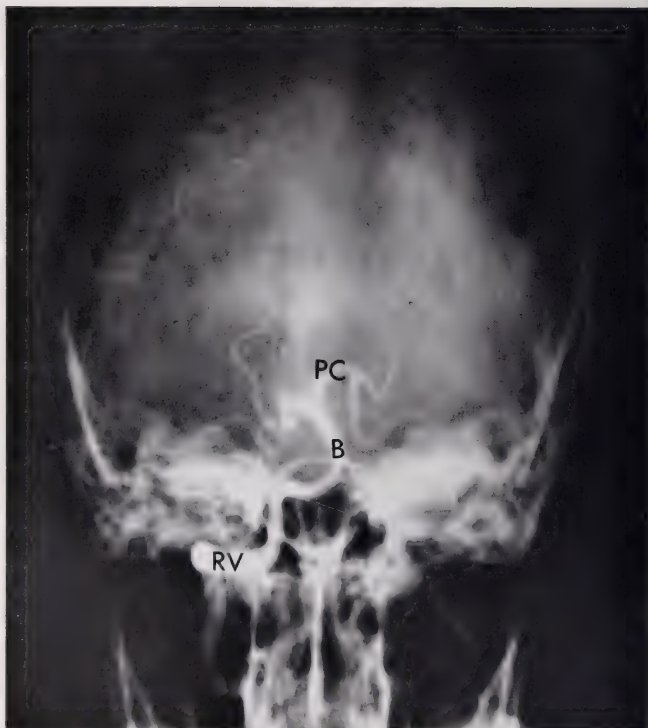


FIG. 3. Right brachial angiogram demonstrates the large right vertebral (RV), basilar (B) and left posterior communicating arteries (PC). Anterior-posterior view.

studies have stressed the leptomeningeal and rete mirabile anastomosis primarily via the external carotid circulation (21).

The patient discussed here had collateral supply only via the posterior circulation and the circle of Willis. Doniger (11) and Wrigley (23) report similar cases with minimal deficits in whom the major collateral contribution was via the posterior circulation. In both, the basilar artery was compromised, the inferior and superior cerebellar arteries were enlarged, and the external carotid system contributed to the collateral supply.

Other patient reports illustrate the variety of clinical signs and symptoms



FIG. 4. Right brachial angiogram demonstrates filling of the vertebral (V) and basilar (B) arteries which supply circulation to the cerebrum via the posterior communicating arteries (PC). Lateral view.

and compensatory vascular changes which occur with carotid occlusions (1-12). In the largest series of carotid artery occlusions secondary to atherosclerosis (16) there were 16 cases of bilateral occlusions out of 646 reported. Thirteen of these had long-standing bilateral carotid artery disease. Those with good collaterals had minimal deficits and those with impaired collaterals had severe deficits. Three patients had old occlusion of one carotid and an acute occlusion on the other side. In another series (8), the mode of onset in patients with bilateral internal carotid artery occlusion was sudden in 6, episodic in 4, and progressive in 1. In none of these cases of bilateral occlusions did symptoms occur prior to those leading to the discovery of the bilateral lesions. Possibly the patient reported here had occlusions of both carotid arteries at the time of the initial hemiparesis 12 years before her present illness.

Grand mal and focal seizures have been observed in unilateral and bilateral carotid occlusive disease (24-26). Symptoms of *epilepsia partialis continua*,

as observed here, have not been reported as a manifestation of bilateral carotid occlusions.

The efficacy of anticoagulants and endarterectomy in cases with carotid occlusion is open to controversy (6-8, 27, 28). The patient in this report did well without such interventions.

Summary

A patient with complete bilateral internal carotid artery occlusions and conspicuously large posterior communicating arteries is described. There was no collateral contribution from the external carotid system and the anterior and middle cerebral circulation was entirely via the enlarged posterior communicating arteries. Symptoms were mild and there was a 12 year interval between an initial hemiparesis and a bout of epilepsy partialis continua which brought the patient to our attention. There was rapid improvement with conservative management.

Acknowledgment

The author is indebted to Dr. I. Kim for interpretation and selection of the radiographs.

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CLINICO-PATHOLOGICAL CONFERENCE

Jaundice and Congestive Failure after Cardiac Valve Replacement

Edited by

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A 44-year-old man was admitted to the hospital for dyspnea, cough, and weakness. At the age of nine he had acute rheumatic fever, and at age 27 he was hospitalized because of fever and rash. He was treated with penicillin for a probable endocarditis. Twelve years later he had an episode of anterior chest pain believed to be a myocardial infarction. Atrial fibrillation was noted one year later. Two years prior to entry he had severe shortness of breath, weakness, and fatigue. Ten months later the aortic and mitral valves were replaced with Starr-Edwards valve prostheses. Following the operation, the patient was improved but subsequently became disabled because of severe dyspnea. Six weeks prior to admission he was hospitalized because of anemia, anterior chest pain, and peripheral edema. No evidence of hemolysis was found, and he continued to receive digoxin, diuretic, and anticoagulant therapy. Several weeks prior to entry he noted anorexia and dark urine. One week before admission a nonproductive cough developed with increasing dyspnea and temperature elevations to 101°F.

He appeared acutely ill. The blood pressure was 105/70, pulse 88 min and irregular, respirations 26/min and temperature 101°F. He was dyspneic sitting upright in bed and his neck veins were distended. The sclerae were icteric and no cyanosis or petechiae were evident. The lungs were clear, and the heart was enlarged to percussion. The point of maximum impulse was in the fifth left intercostal space in the anterior axillary line. A grade II early blowing diastolic murmur was heard at the third left intercostal space, and an intermittent high-pitched nonholosystolic murmur was also present at the apex. The prosthetic valve sounds were normal.

The liver was felt four fingerbreadths below the right costal margin, and the spleen was not palpated. The femoral and pedal pulses were normal. No edema, clubbing, or calf tenderness was present.

The hemoglobin was 9.5%, the white blood count 12,150 with 66% neutrophilic leukocytes, 2% band forms, 31% lymphocytes, and 1% monocytes. The red blood cells showed moderate polychromasia, poikilocytosis, and hypochromia. The platelet count was 208,000/mm³ and the reticulocyte count 5%. The urine specific gravity was 1.014 and the sediment contained more than 30 red blood cells and 3 to 4 granular casts per high power field. No red blood cell casts were present. The urine contained bilirubin and urobilinogen in a dilution of 1:20. The erythrocyte sedimentation rate was

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44 mm/hr. The blood urea nitrogen was 42 mg%, and the blood sugar 108 mg%. The serum sodium was 130 mEq/l, potassium 4.2 mEq l, chlorides 87 mEq/l, and carbon dioxide 29.5 mEq/l. The total serum bilirubin was 3.4 mg% with 2.6 mg% direct reacting. The serum alkaline phosphatase activity was 8.9 Bessy-Lowry units, the scot 48 units, and prothrombin time 19 seconds (control 12 seconds). The serum albumin was 4.0 gm% and globulin 2.7 gm%. Three blood cultures were sterile. A Coombs' test was negative.

A chest x-ray showed the heart to be enlarged with prominence of the left ventricular border. The pulmonary vasculature was prominent bilaterally, and the lungs were clear. The electrocardiogram demonstrated atrial fibrillation, with occasional ventricular premature contractions. There was right axis deviation, ST segment depression, and biphasic T waves in leads 2, 3, aVF and V₅-V₆.

Digoxin and anticoagulant therapy was continued. The following day he was afebrile. He lost three pounds of weight during the first three days. The neck veins were distended and pulsatile, and the venous pressure was 240 mm H₂O and the circulation time was 45 seconds. There was a slight improvement in his clinical condition, and he was no longer dyspneic at rest; but did not lose any further weight with intermittent mercurial injections or daily chlorothiazide. The liver remained enlarged and pulsatile in systole. A right heart catheterization was performed on the 20th hospital day. The right atrial pressure was 20 mm Hg, the right ventricular and pulmonary artery pressures were 120 mm Hg and the pulmonary wedge pressure was 40 mm Hg with a very tall V wave. A retrograde aortic catheterization demonstrated a small regurgitant jet. The half-life of Cr⁵¹ tagged red cells was 20 days, consistent with mild hemolysis. One week later, repair of a 2 cm dehiscence of the posterior rim of the mitral Starr-Edwards ball valve was performed. At surgery, prior to the operative repair, the right atrial pressure was 41/9 mm Hg (mean 25), right ventricle 70/7 mm Hg, left atrium 75/18 mm Hg with a high V wave and brachial artery 112/72 mm Hg. The aortic ball valve was intact and the tricuspid valve was normal but functionally incompetent. Postoperatively the apical and parasternal murmurs disappeared, but a soft, early diastolic blowing murmur persisted at the left sternal border. He received penicillin and streptomycin therapy, but developed a low grade fever with occasional elevations to 102°F. A chest x-ray showed an infiltrate in the right lung base and fluid in the right costophrenic angle. During the second postoperative week, he lost ten pounds of weight and the liver decreased considerably in size. Slight edema of the ankles persisted. Several blood cultures were sterile and a repeat of the chest x-ray showed clearing of the infiltrate in the right base, but persistence of the right pleural effusion. The hemoglobin was 10 gm%, and the white blood count 10,800 with a shift to the left. He remained febrile and tetracycline therapy was begun. On the 31st postoperative day, he suddenly developed chest pain and became unresponsive. An electrocardiogram showed ventricular fibrillation. He was treated with closed cardiac massage and external defibrillation. He remained coma-

tose and repeat electrocardiograms showed atrial fibrillation with multiple ventricular contractions and runs of ventricular tachycardia. Two days later cardiac arrest recurred, and he died on the 33rd postoperative day. A blood culture drawn several days earlier grew *Alcaligenes fecalis*.

*Dr. Richard P. Lasser**: Let us begin with an analysis of certain aspects of this patient's history. In addition to chronic heart disease, he is said to have had a myocardial infarction at 39 years of age. The clinical syndrome interpreted as myocardial infarction could have resulted from a coronary artery embolus. Myocardial infarction may occur without coronary disease due to aortic insufficiency, with a wide pulse pressure and low diastolic pressure. However, usually in this circumstance, there is a history of severe decubitus angina. Severe aortic stenosis also can produce myocardial infarction without occlusion. These infarcts are usually subendocardial. On the other hand, angina-like chest pain occurs in patients with mitral valve disease and pulmonary hypertension. This pain occurs with effort, is more protracted than typical angina, and may not respond to nitroglycerine. It is believed due to right ventricular ischemia-angina of the right ventricle. Therefore, mitral stenosis with severe pulmonary hypertension can produce a syndrome mimicking myocardial infarction, and it is not unlikely that this is the explanation in this patient.

Two years prior to admission he developed severe shortness of breath, weakness, and fatigue due to left ventricular failure, with pulmonary congestion. Atrial fibrillation was noted. Since aortic stenosis or aortic insufficiency alone only occasionally produces auricular fibrillation, this suggests significant involvement of the mitral valve, even though the distinctive murmurs of mitral stenosis are not described. Ten months later, this valve as well as the aortic valve was replaced. Because it is not uncommon to underestimate the degree of aortic insufficiency prior to the time of mitral valve surgery, two valves may have to be repaired, even though one has anticipated only single valve involvement. Mitral stenosis protects against the hemodynamic effects of aortic insufficiency; since the stroke volume is very small, the cardiac output is low and there is not much regurgitation. The murmur may be so quiet that it is disregarded. However, once the mitral valve is repaired, a mild aortic insufficiency is aggravated and aortic repair must also be performed.

The patient was improved following the operation, but subsequently became disabled because of severe dyspnea, developed severe heart failure, a diastolic, blowing murmur, and an intermittent high-pitched nonholosystolic murmur. The prosthetic valve sounds were normal which is an important observation since a clot on either one of the valves might alter these sounds. Clotting of the prosthetic valves occurs in about three percent of prosthetic valve implantations and is usually a cause of rapid demise. It may occur with or without anticoagulant therapy.

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The diastolic murmur heard along the left sternal border may be the clue which would explain his very severe failure. If he had a partial dehiscence or partial rupture of the prosthetic aortic valve, the murmur would be due to aortic insufficiency. With aortic insufficiency, he would have left ventricular decompensation. This, of itself, can produce dysfunction of the prosthetic mitral valve due to a high diastolic pressure in the left ventricle. Starr and DeBakey have noted diastolic murmurs postoperatively in about 25 percent of patients with aortic implants. In a small number, dehiscence was noted. Some amount of regurgitation must occur, but cannot always be demonstrated. Only when there is severe failure or a loud murmur are aortic angiograms performed to actually demonstrate a regurgitation jet.

The diastolic murmur which was heard might also represent pulmonic insufficiency, secondary to pulmonary hypertension. This, however, should diminish, not increase after mitral valve replacement.

The nonholosystolic murmur at the apex probably resulted from disruption of the mitral valve sutures. Mitral valve dehiscence is another significant cause of death following prosthetic valve implantation.

In all likelihood, the marked icterus was due to congestive failure, with tricuspid insufficiency producing acute distention of the liver. A cholestatic type of jaundice is common in heart failure. It has been proposed that if the biliary secretory pressure is exceeded by a very high systemic venous pressure (and therefore a high hepatic venous pressure), there may be impairment of biliary secretion. The jaundice might be a reflection of serum hepatitis, although the incubation period would be extremely long. Infectious hepatitis is also possible, though congestive failure is the most likely cause.

Anemia is another complication of valve implantation. Hemolytic anemias have been described following prosthetic repair and teflon patches, but usually they are mild. The anemia may be severe where there is a dehiscence of the valve. It is believed that the very high speed jet breaks the red cells and causes a form of the so-called microangiopathic anemia. Usually, this is accompanied by a shortening of the red cell survival time.

The marked hematuria needs an explanation. Profound failure, as well as anticoagulant therapy can of course produce hematuria. However, since thromboembolism is a well known complication of prosthetic valve implantation, I would not be surprised if he had renal infarcts. This might account for the moderate azotemia which could also be accounted for by the profound heart failure.

The electrocardiogram showed a right axis deviation consistent with mitral valve disease and pulmonary hypertension. The right heart catheterization performed postoperatively showed very marked pulmonary hypertension, higher than the systemic pressure. This indicated a chronic state of pulmonary hypertension, secondary to mitral valve disease, which did not resolve following the operation. The very tall V wave in the left atrial pressure curve represents a regurgitant jet and indicates dehiscence of the prosthetic valve. The retrograde aortic catheterization disclosed a small amount of aortic

insufficiency. With these findings, repair of a 2 cm dehiscence of the mitral valve was performed.

Following the second operation the patient's failure resolved and he seemed improved, but was febrile. Blood cultures were sterile. Endocarditis, another complication of valve surgery, should always be suspected. The only sign of a superimposed bacterial endocarditis may be a low-grade fever. The patients with endocarditis following prosthetic valve replacement are generally not very sick and show only a few red cells in the urine. The spleen is usually not enlarged and splinter hemorrhages and petechiae are uncommon. Since he was febrile for a prolonged period of time without apparent reason, I think endocarditis was present. These days, most patients receive large doses of prophylactic antistaphylococcal antibiotic agents pre- and postoperatively to inhibit seeding by *Staph. aureus*. About two-thirds of the cases of endocarditis are caused by *Staph. aureus*. Finally, in this case, *Alcaligenes fecalis* was cultured and I believe that this was the responsible organism. Since other cases have been reported with this particular organism, it cannot be considered a contaminant. Previously, 3.6 percent of patients died postoperatively from fatal endocarditis. Since the extensive use of prophylactic antibiotic therapy, the mortality has been reduced to 0.2 percent.

The patient's death can be explained by a number of mechanisms. He could have had a coronary embolism. Coronary embolization is a definite complication of prosthetic implantation, since clots usually form around the ring or on struts of the valve itself, particularly if endocarditis is present.

In conclusion, I think he had chronic rheumatic heart disease, with replacement of the mitral and aortic valves by prosthetic devices. Dehiscence of the prosthetic valves led to mitral and aortic insufficiency, and to profound heart failure. The liver was congested with central lobular necrosis and bile stasis secondary to the severe failure. In addition he had renal infarctions. He also had pulmonary hypertension with pathological changes in the pulmonary arterial tree. Finally, he developed bacterial endocarditis and succumbed following a coronary embolism.

*Dr. Kalman Feinberg**: Thank you, Dr. Lasser. Are there any questions?

Speaker from the Floor: In a recent Journal of The American Dental Association, two patients died as a result of valvular dislodgement from bacterial endocarditis. The bacteremia followed a dental procedure.

Dr. Lasser: This is certainly possible. Any dental procedure or urinary tract procedure can produce a bacteremia. However, once the valve is endothelialized, the incidence of bacterial endocarditis drops very significantly. Therefore, if prophylaxis is maintained for three weeks, the incidence of endocarditis will be significantly decreased.

Dr. Feinberg: At autopsy, no cutaneous lesions were noted, and the pleural and peritoneal cavities were free of fluid.

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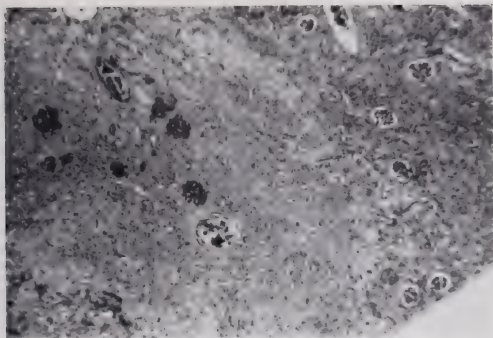


FIG. 1. Infarct of kidney showing necrotic glomeruli and tubules (hematoxylin and eosin $\times 100$).

The spleen was markedly enlarged, weighing 800 grams. The capsular surface contained focal areas of calcified deposits, indicating an old perisplenitis. The parenchyma was firm, purple, and congested. At one pole there was a well-circumscribed, firm, yellow lesion with puckering of the overlying surface, which microscopically was an organizing nonseptic infarct.

The kidneys were slightly enlarged and in the upper pole of the right kidney there was a small acute infarct (Fig 1). The remaining glomeruli were infiltrated by acute inflammatory cells. This reactive glomerulitis was due to the septicemia. There was also marked deposition of iron in the proximal convoluted tubules, indicating an intravascular hemolysis, presumptively secondary to the prosthetic valves.

The liver was enlarged, weighing 2,500 grams. On section, the hepatic veins were dilated and the walls were sclerotic. The parenchyma was brown and firm. There was centrilobular atrophy of the parenchymal cells, and fibrosis around the central veins consistent with chronic passive congestion. A large number of acute inflammatory cells were found in the portal tracts, and hepatic sinusoids, with areas of focal liver cell necrosis and acute inflammatory cells reflecting a generalized septicemia. No organisms were found in these areas. An iron stain revealed iron in the Kupffer cells secondary to hemolysis.

The lungs showed sequelae of mitral valve disease. They were reddish brown and firm. There was marked intimal fibrosis of the large pulmonary arteries and proliferation of the elastic fibers in the smaller arteries, typical of chronic pulmonary hypertension. The alveolar septums were fibrotic, and the alveoli contained iron-laden macrophages as a result of rupture of pulmonary capillaries and bronchial veins.

The heart was markedly enlarged, weighing 810 grams. The resected aortic and mitral valves revealed old rheumatic disease. The tricuspid and pulmonary

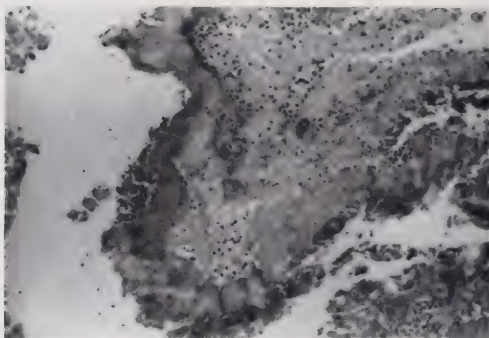


FIG. 2. Septic thrombus on prosthetic mitral valve. Bacterial colonies are abundant along the surface of the thrombus (hematoxylin and eosin $\times 100$).

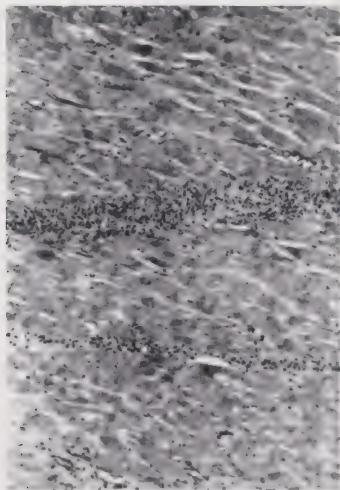


FIG. 3. Myocardial infarct showing ischemic necrosis of myocardial fibers and an acute inflammatory cell infiltration (hematoxylin and eosin $\times 100$).

valves were unremarkable. The right ventricle was hypertrophied and dilated. The pulmonary outflow tract and left atrium were also dilated. The Starr-Edwards valves were intact. A thrombus was attached to the atrial side of the prosthetic mitral valve and partially occluded the opening. Microscop-

ically, the thrombus contained clumps of gram-negative bacteria which on culture proved to be *Alcaligenes fecalis* (Fig 2). The left ventricle was dilated and hypertrophied. There were patchy areas of subendocardial fibrosis. The posterior lateral wall contained an acute infarct which extended from the base of the mitral valve to near the apex (Fig 3). The remaining myocardium revealed hypertrophy with scattered areas of fibrosis and myocytolysis. The coronary arteries disclosed only a minimal degree of atherosclerosis.

Final Diagnoses:

1. CHRONIC RHEUMATIC CARDIOVALVULAR DISEASE.
2. ACUTE SEPTIC THROMBOSIS OF MITRAL VALVE PROSTHESIS (*Alcaligenes fecalis*).
3. RECENT INFARCTS OF SPLEEN AND RIGHT KIDNEY.
4. ACUTE MYOCARDIAL INFARCT OF POSTEROLATERAL WALL OF LEFT VENTRICLE.

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Unusual Problems in Surgery

CASE NO. 15

Splenosis and Intestinal Obstruction

Autotransplantation of splenic tissue within the peritoneal cavity following traumatic rupture of the spleen has been termed "splenosis" (1). Although the implanted splenic nodules are usually numerous and widespread, they rarely produce symptoms. In most of the 52 reported cases, splenic implants were discovered at postmortem examination or during surgery for other conditions (2-15). The following case is an example of intestinal obstruction which was caused by splenosis.

CASE NO. 15

A 12-year-old girl was admitted to Elmhurst Hospital on May 15, 1967 because of abdominal pain. Two days before admission to the hospital she began to have episodes of colicky lower abdominal pain and vomiting. She was given an enema at home which resulted in the passage of a small amount of stool. The colicky abdominal pain persisted but never became localized.

PAST HISTORY: In August, 1964 the patient fell down a flight of wooden steps and subsequently complained of a pain in the region of her left lower ribs. She was admitted to Elmhurst Hospital. After a period of observation the diagnosis of traumatic rupture of the spleen was made and the patient was operated upon. The peritoneal cavity contained 200 cc of blood. Lacerations of the superior and inferior poles of the spleen were found and splenectomy was performed.

From the Department of Surgery, The Mount Sinai Hospital, New York, N. Y., and The Mount Sinai Services at City Hospital Center, Elmhurst, Queens, N. Y.

The postoperative course was relatively uneventful. The child remained well until the onset of her present symptoms.

PHYSICAL EXAMINATION: The patient was a well-nourished, well-developed girl complaining of abdominal pain and appearing somewhat dehydrated. Her temperature was 99°F.; pulse rate was 96 per minute; respiratory rate was 22 per minute and her blood pressure was 110/70 mm Hg. Pertinent physical findings were limited to the abdomen. A well-healed left paramedian upper abdominal surgical scar was present. The abdomen was soft, slightly distended, and generally tender, but no rebound tenderness could be elicited. No masses were palpable within the abdomen. The bowel sounds were hypoactive. The rectum was empty. Laboratory studies on admission revealed the following values: Hemoglobin 12.4 gm/100 cc; white blood cell count, 13,300/cu mm with 64% neutrophils, 5% stabs, 29% lymphocytes and 2% monocytes. The urinalysis was normal. X-ray films of the abdomen showed several distended loops of jejunum containing air-fluid levels and some gas in the splenic flexure of the colon which indicated a partial small intestinal obstruction.

HOSPITAL COURSE: The patient was treated with intravenous fluids and nasogastric decompression. Rehydration was accomplished after several hours. Conservative treatment was then continued in the hope that the partial obstruction might be relieved with nasogastric decompression. X-ray films of the abdomen after 12 hours of therapy revealed increased distention of the small bowel loops and no gas in the colon. (Fig. 1A, 1B)

An exploratory laparotomy was performed through an extension of the previous left paramedian incision. A small amount of clear amber fluid, which was sterile on culture, was present in the peritoneal cavity. The peritoneum beneath the incision was completely free of adhesions. The jejunum and upper portion of the ileum were markedly distended, and a mass of col-

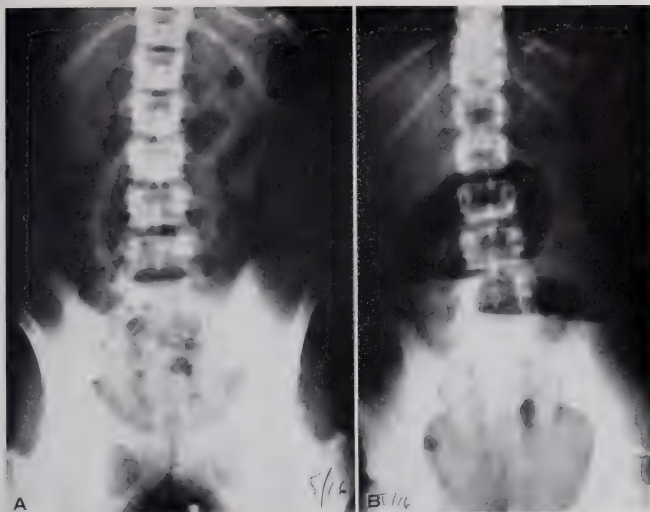


Fig. 1A and B. Abdominal x-rays taken in the supine and upright positions show evidence of small bowel obstruction.

lapsed small bowel loops was present in the right lower abdomen. Approximately 30 purple nodules, ranging in size from 1 mm to 1½ cm were present in the greater omentum and on the serosa of the jejunum and ileum. (Fig. 2) The greater omentum was adherent to several implants on the serosa of the upper ileum which produced a kinking and subsequent obstruction of the bowel. The obstruction was relieved by freeing the omentum from the intestine. A specimen of the nodule bearing omentum was excised for histologic study.

The postoperative course was complicated by a right lower lobe pneumonia which responded promptly to antibiotic therapy. Recovery was complete and the patient was discharged on the 10th postoperative day. She has remained asymptomatic.

PATHOLOGY REPORT: The specimen of omentum measured 6 cm x 2 cm x 2 cm and contained two nodules measuring 1½

cm x 1 cm x ½ cm and several other nodules measuring 2 to 3 mm in diameter. (Fig. 3) All were of firm consistency and dark red color. Microscopic examination showed loose fibroadipose tissue containing ovoid and lobulated masses of splenic tissue which were composed of a vascular red pulp with prominent sinusoids. There were numerous Malpighian follicles with prominent germinal centers, some of which had no central arterioles. (Fig. 4) The diagnosis was splenosis and chronic inflammation of the omentum.

Discussion

The first cases of splenosis were reported in 1896 by Albrecht (16) and in 1907 by Schilling (17). In both instances numerous splenic nodules were found at autopsy. There was no his-



Fig. 2. Operative photograph showing splenic implants on the serosal surface of the small bowel (arrows).

tory of trauma or splenectomy in either case and the nodules were regarded as accessory spleens. In 1910 Von Kuttner (18) performed an autopsy on a patient who had had his spleen removed four years earlier because of splenic rupture. He found multiple splenic nodules which he considered to be accessory spleens. In 1911, Faltin suggested that the splenic nodules were actually implants (19). Waugh, in 1946, was the first to recognize this phenomenon during a laparotomy (which was performed five years after splenectomy) (20).

There have been numerous attempts

to explain the presence of intra-abdominal splenic implants. The autotransplantation theory, which maintains that the nodules are implants of splenic fragments which had been dispersed throughout the peritoneal cavity, is the most widely accepted and is supported by experimental studies. Von Stubenrauch reported experimental work in which crushed splenic pulp was placed within the peritoneal cavities of splenectomized dogs (21). Peritoneal splenic implants were demonstrated at autopsy three months later. Implantation of splenic tissue requires two or three weeks in

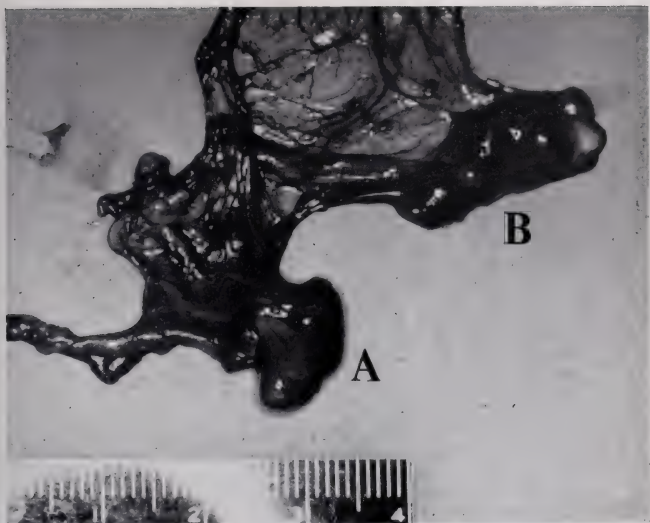


Fig. 3. Resected omentum. Note single (A) and multiple (B) nodules of splenic tissue.

rats (22) and six months in rabbits (23). Splenosis has been found as early as six months after splenic rupture in man (24).

Splenic implantation most frequently occurs on the serosa of the small intestine, the greater omentum, parietal peritoneum, large intestines, and mesentery of the bowel. However, the surfaces of any of the intraabdominal organs may be the site of implantation. Splenic transplantation in the subcutaneous tissue and even in the chest wall has been reported (25). The nodules may vary in color from pink to dark red or greenish black. Peritoneal splenosis has been mistaken for endometriosis, metastatic carcinoma, sarcoma, and angiomas of

the bowel wall. Microscopically, the implant may have all the constituents of normal spleen or only the red pulp to identify it as splenic in origin. The nodules are numerous, not infrequently numbering over 100. They vary in size from pinpoint to 2 cm in diameter and rarely have a pedicle. The hilus is absent and the blood supply usually originates from small vessels which enter the capsule at its periphery. Within the capsule itself, which is thick and fibrous, smooth muscle and elastic tissue are decreased in amount or absent. The red pulp is normal. The Malpighian corpuscle does not ordinarily have a central artery.

In contradistinction to splenic

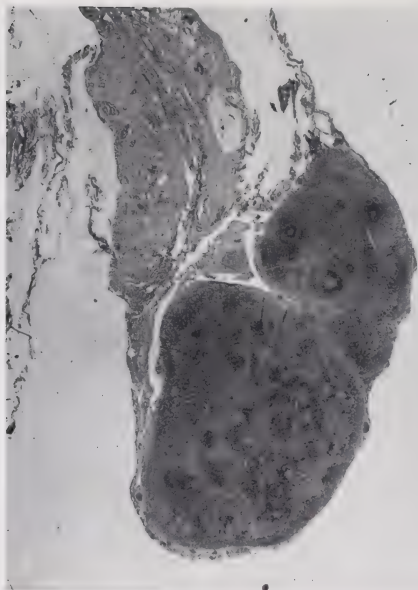


Fig. 4. Low power photomicrograph of a splenic nodule showing vascular red pulp with prominent sinusoids and numerous Malphigian follicles.

transplants, accessory spleens arise during the embryological period of development and resemble the structure of the principal spleen. The microscopic anatomy is that of normal splenic tissue. Accessory spleens are usually located at the hilus of the principal spleen, the splenic pedicle, the gastrosplenic ligament, the retroperitoneal region near the tail of the pancreas, the greater omentum, the splenocolic ligament, and the mesentery of the large and small bowel. Over 75% of accessory spleens are found in the immediate vicinity of the

splenic hilus and pedicle (3). The number of accessory spleens is usually limited to one or two but in rare instances as many as ten have been found. The average accessory spleen is larger than transplanted splenic tissue and may be 5 cm or more in diameter.

Stobie has shown that implanted splenic tissue is capable of function (26). In 1947, he reported a case of congenital hemolytic icterus in which the spleen was torn during splenectomy. Hemolytic anemia recurred and at laparotomy four years following

splenectomy, multiple splenic implants were found in the abdominal cavity.

A review of the 52 reported cases reveals that splenosis most commonly occurs in the second and third decades of life. Symptoms, when present, are vague (3). The occasional episodes of abdominal cramps or discomfort which are sometimes present are believed to be caused by adhesions, which are common, and frequently extensive (13). Most patients have had a splenectomy because of splenic trauma or a hematologic disorder. The interval between splenic injury and the diagnosis of splenosis ranged from six months to thirty years. The diagnosis of splenosis is usually made at autopsy or during surgery for unrelated conditions, such as appendectomy, repair of incisional hernia, hysterectomy, and cholecystectomy. Surgery was performed in nine cases because of intestinal obstruction. In all but one of these cases adhesions were responsible for the obstruction and not the splenosis per se. The only previously reported instance in which intestinal obstruction was directly due to splenic implants is the case reported by Cotlar and Cerise in 1959 (3).

Although only 52 cases of splenosis have been reported in the literature, the actual incidence of the disease is probably greater. Patients who have survived traumatic rupture of the spleen and have experienced asymptomatic splenosis may not be subject to a second operation or to autopsy. Although splenosis usually produces few symptoms, intestinal obstruction may be caused either as a direct result of the splenic implants or as a

result of adhesions following splenectomy.

Chalasani Prasad and A. Robert Beck

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Coronary Artery Disease: Rest, Repair or Replacement*

DWIGHT E. HARKEN, M.D.**

Dr. Arthur Master, you are immortalized by so many things that you will forgive my personal pleasure in addressing *you*, the mortal master. Hopefully, many, many of these salutes will pass before they become memorial lectures.

We who know you personally, try by these lectures to share you with the world that knows you only through publications, now spanning forty-five uninterrupted years (1923–1968). You may know that you have published something *every* year for forty-five years! This year will see you over your 400th publication. Indeed you have overcompensated for those lean years when establishing a *new* man, in a *new* practice, in a *new* field in New York, 1926, 1927, and 1928. Arthur, do you realize that you had only one publication in each of those years? You recall those no doubt as hard, hustling years but a study of your life through the printed page counts them as the “quiet hours!” You defied custom: you did not perish!

Our subject is coronary artery disease. There are descriptions and illustrations of men with coronary artery disease centuries B.C.E. (Fig. 1).

Shakespeare, in the death of Falstaff (Fig. 2) described the syndrome that we call “cardiogenic shock.” It was all there (Fig. 3): hypovolemia (“nose like a pen,”) poor cardiac output, vasoconstriction and metabolic acidosis (“legs as cold as any stone,”) aberrant and obtunded cerebral activity (“muttered of greenfields”) from CO₂ narcosis and anoxia (“smiled upon his finger ends,”) and so a complete and classical clinical description.

Shakespeare also described sudden death from coronary occlusion in the quick demise of King Lear. He had had previous pain in the chest.

Matthew Baillie in 1798 in his MORBID ANATOMY, presented an engraving of heart “where a part of the left ventricle near the apex was dilated into an aneurysmal sac.” In 1815 Joseph Hodgson of Birmingham in DISEASES OF ARTERIES, noted softened muscle in the case of a woman who died suddenly. “The coronaries were calcareous tubes.” He also described *rupture of the heart*. It was clearly evident that some of Heberden’s cases in 1768 were affected by coronary thrombosis; the duration and occasion of the pain makes that clear (Fig. 4).

* Presented as the Arthur M. Master Lecture, March 28, 1968, The Mount Sinai Hospital, N.Y., N.Y.

** Clinical Professor of Surgery, Harvard Medical School; Chief of Thoracic Surgery, Peter Bent Brigham and Mount Auburn Hospitals.

The author regrets and assumes responsibility for the poor quality of the illustrations. It was necessary to lift them from lantern slides and 16 mm films.



FIG. 1. Patient clutching his chest, going down to death, the distraught family are nearby. This frieze is from the Hyksos period, the time of the first Israelian occupation of Egypt. Perhaps this Egyptian townfather's emotional response caused his coronary occlusion.

Leyden in 1833, gave a lucid, scientific account of coronary occlusion as a clinical entity but it was little appreciated.

It was in 1845 that Peter Latham of St. Bartholomew Hospital published his *Lectures on the Heart* full of acute observations and fine clinical descriptions.

In 1878 Adam Hammer, a German refugee in St. Louis, published one of those perfect descriptions of coronary artery disease that was little noticed but unsurpassed.

Herriek gave us the classical description with case reports in 1912. But this was really not seen even though it was the lead article in the *Journal of the American Medical Association*, December, 1912 (Fig. 5). In short, "We see what we look for and we look for what we know."

Characteristic of this axiom is the fact that Dr. Henry Christian, Hersey Professor of Medicine at Harvard and Physician-in-Chief at the Peter Bent



FIG. 2. Falstaff: gay, obese, gouty, indolent, undisciplined just before he died off-stage.

Act II Scene III

41

Bard. Would I were with him, wheresome'er he is,
either in heaven or in hell!

Host. Nay, sure, he's not in hell: he's in Arthur's bosom,
if ever man went to Arthur's bosom. A' made a finer end
—and went away an it had been any christom child; a'
parted even just between twelve and one, even at the
turning o' the tide: for after I saw him fumble with the
sheets and play with flowers and smile upon his fingers
ends, I knew there was but one way; for his nose was as
sharp as a pen, and a' babled of green fields. "How now,
Sir John?" quoth I: "what, man! be o' good cheer." So
a' cried out "God, God, God!" three or four times: now
I, to comfort him, bid him a' should not think of God, I
hoped there was no need to trouble himself with any
such thoughts yet. So a' bade me lay more clothes on his
feet: I put my hand into the bed and felt them, and they
were as cold as any stone; then I felt to his knees, and so
upward, and upward, and all was as cold as any stone.

Nym. They say he cried out of sack.

Host. Ay, that a' did.

Bard. And of women.

Host. Nay, that a' did not.

Boy. Yes, that a' did; and said they were devils incarnate.

Host. A' could never abide carnation; 'twas a colour he
never liked.

Boy. A' said once, the devil would have him about women.

Host. A' did in some sort, indeed, handle women; but then
he was rheumatic, and talked of the whore of Babylon.

Boy. Do you not remember a' saw a flea stick upon Bar-
dolph's nose, and a' said it was a black soul burning in
hell-fire?

FIG. 3. Bardalot asked Host about Falstaff's death in *Henry IV*. Host delivers what may have been the first classical description of cardiogenic shock.

Brigham Hospital, was present at Herrick's presentation of his classic description establishing sudden obstruction of the coronary arteries as a clinical entity, yet did not regard it worthy of bringing it to the attention of his young associate, Samuel A. Levine. Young Samuel had to make history all over again and acquaint the clinicians of this country with this condition in 1929.

While chronicling the classical descriptions of coronary artery disease, let

TRANSACTIONS.

*VI. Some Account of a Disorder of
the Breast.* By WILLIAM HEBER-
DEN, M. D. F. R. S.

Read at the COLLEGE, JULY 21, 1768.

THERE is a disorder of the breast, marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, of which I do not recollect any mention among medical authors. The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called *Angina pectoris*.

THOSE, who are afflicted with it, are seized, while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would

FIG. 4. First page of Heberden's treatise and first use of term *angina pectoris*.

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CLINICAL FEATURES OF SUDDEN OBSTRUCTION OF THE CORONARY ARTERIES

JAMES B. HERRICK, M.D.
CHICAGO

Obstruction of a coronary artery or of any of its large branches has long been regarded as a serious acci-

The coronaries are not so strictly end-arteries, i. e., with merely capillary anastomoses, as Cohnheim and others thought. By careful dissections, by injection of one artery from another, by skiagraphs of injected arteries and by direct inspection of hearts made translucent by special methods, there is proof of an anatomic anastomosis that is by no means negligible.

Jamin and Merkel's† beautiful stereoscopic skiagraphs show the remarkably rich blood-supply of the heart,

FIG. 5. Herrick's classic description from JAMA.

me digress to acquaint you with *an hitherto unidentified case report* that has interesting temporal coincidence with your life, Dr. Master. The year is your fateful 1923, the year of your first publication, THE ELECTROCARDIOGRAM AND HEART MUSCLE DISEASE. This case report for the same year is that of Mr. X, *to this moment not publicly identified*. As Mr. X, this important man died in 1923. Dr. John Sampson reported Mr. X's death in terms of Herrick's classical description of coronary artery obstruction in 1940 (Fig. 6). It is unnecessary to review Herrick's description; it is identical with that of Mr. X (Fig. 6).

Now that the several physicians, friends, and consultants involved have passed on, Dr. Sampson has permitted me to identify Mr. X tonight (Fig. 7).

It was *President Warren G. Harding*. Here is Dr. Sampson's hand-written personal communication. One cannot take seriously ever again the scurrilous reports that suggested murder or worse (Fig. 8).

"Scandal as it had clouded Warren G. Harding's life, haunted his death."
(Adams)

* * *

Enough of preliminaries. Let us review some specific surgical advances that relate to Dr. Master's activities. *The theme tonight will be the objective evaluation of surgery, not surgical techniques*. Five questions will be asked:

First, what objective studies support mammary artery implantation for coronary artery disease?

Second, what is the need for, and nature of, the demand pacemaker in heart block?

Third, how do we define and treat severe mitral insufficiency from the papillary muscle syndrome?

Four, what is the surgical area in managing ventricular aneurysms as an end phase of coronary artery disease?

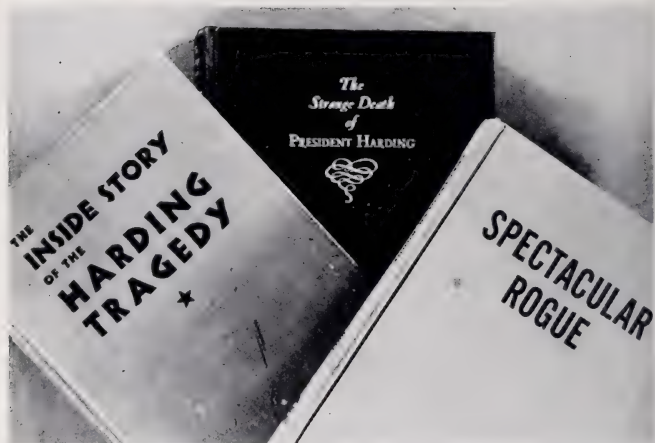


FIG. 8. Books relating to President Warren G. Harding's "mysterious death."

Fifth, what is the current position in cardiac assistance and heart replacement?

As we address ourselves to these five areas, we shall ask, in the tradition of Master: What facts support the place for surgery now or perhaps in the future? This is reminiscent of the old Scottish expression, *facts are chieft that rinna ding*, meaning roughly that facts are like bad children that do not necessarily do what you want them to do.

I. Internal Mammary Artery Implantation for Angina

Here the cardinal questions are: Does the implanted artery remain patent? Does the new blood supply perfuse the myocardium in a normal coronary arterial blood pattern? Is sufficient blood volume delivered to correct ischemic heart disease? Is the mortality and morbidity acceptable? Is comfortable life prolonged?

Credit for the original concept of mammary artery implantation goes to Dr. Arthur Vineberg. Recognized for the initial proof of patency is Dr. Mason Sones in his angiogram of a patient operated by Dr. Vineberg eight years previously. That cineangiogram will be shown here tonight. For extension of elegant surgical technique, we recognize Drs. Favaloro, Effler, and Warren J. Taylor. For myocardial distribution, the studies of Drs. Gorlin and Taylor of the Peter Bent Brigham Hospital are outstanding. And again, we recognize Dr. Gorlin and his colleagues at the Brigham for the superb metabolic studies that prove the correction of anaerobic myocardial metabolism which is, after

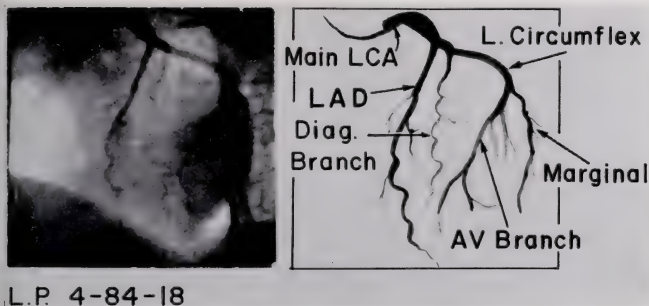


FIG. 9. Left coronary artery angiogram and anatomic key. (Courtesy of Drs. Kemp and Gorlin)

all, ischemic heart disease. The proof of this reversal from anaerobic to aerobic or the nonischemic state is by lactic acid studies. To attain these with exemplary mortality and morbidity figures, we use the figures in the first one hundred implants of the Thoracic Service at the Brigham with special recognition of Dr. Taylor as surgeon and Dr. Leroy Vandam, the Professor of Anesthesiology. That *life is prolonged* is likely as based on those same first one hundred patients.

The cornerstone of medical and surgical evaluation is complete coronary angiography in at least two views. The anatomy of these arteries must be thoroughly understood and the pathologic patterns classified by repeated defec clarification.

The anatomic work charts show what we are looking for and in such charts as these are marked the location and extent of the lesions (Figs. 9, 10).

These brief cineangiograms show normal coronary arteries and then some coronary artery disease patterns.* Later, Sones' historic study of Vineberg's operation will be shown (Fig. 14).

Having visualized the arteries and their abnormalities objectively by angiography, we can demonstrate the technique of implantation—not just to revascularize the front of the heart but the posterior myocardium as well by bilateral internal mammary artery implantation.†

The moving picture summarizes and demonstrates the technique of implanting the right internal mammary artery under the *left anterior descending* coronary artery anteriorly and on the left. The diaphragmatic aspect of the left ventricle is revascularized by the left internal mammary artery† (Figs. 11, 12, 13).

* At this point Dr. Harken showed selective angiograms from Dr. Richard Gorlin's Laboratory.

† At this point Dr. Harken showed colored movies of bilateral internal mammary implantation.

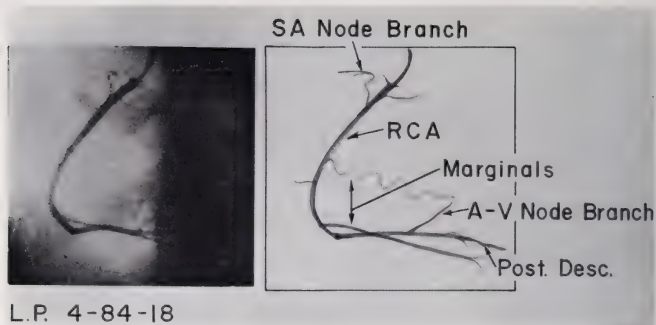


FIG. 10. Right coronary artery angiogram and anatomic key. (Courtesy of Drs. Kemp and Gorlin)



FIG. 11. A frame from the colored moving picture showing three spurting divisions of the isolated internal mammary artery. Both right and left mammary arteries are freed via sternal split incision.



FIG. 12. The heart is lifted to expose the diaphragmatic surface. A tunnel is carried under the posterior descending artery for posterior implantation of the left mammary artery. (frame from the movie)

Having demonstrated the method of angiographic disease mapping and the operation of revascularization, the next question is: Can these mammary artery implants remain patent? To this we reply with that historic first cineangiogram on Vineberg's patient, eight years after surgery* (Fig. 14). This was performed by Dr. Mason Sones.

The cineangiogram shows not only patency but retrograde filling of the *left anterior descending* artery. It also demonstrates that the *left anterior descending* artery cannot be filled from the left coronary artery stoma at the aorta. This *first* proves that the implants can remain open.* Subsequent studies on our patients by Gorlin (and Sones' studies as well) indicate that when patients are properly selected and operated, patency persists in over eighty percent.

Now you inquire as to the flow pattern taken by the blood delivered to the myocardium by the implant. Where does the new blood supply go? Does it rush directly into the heart chamber? Does it bypass the myocardium by arteriovenous shunts? Or, does it perfuse the myocardium in a pattern similar to normal coronary arterial blood supply? Again, Gorlin provides the objective answer. He has shown that the disappearance of Krypton 85 from the myocardium is similar whether it gets to that heart muscle via mammary implant or by coronary artery (Fig. 15).

* At this point Sones' classical angiographic "first" was shown. This demonstrated patency years after Dr. Vineberg's operation.



FIG. 13. A double tunnel is carried by incision under the left anterior descending artery (A) and on the left surface of the left ventricle for implanting the right mammary artery. (B) (frames from the movie)



FIG. 14. Sones' classical "first" angiogram demonstrating patency of the mammary artery 8 years after myocardial revascularization by Dr. Vineberg.

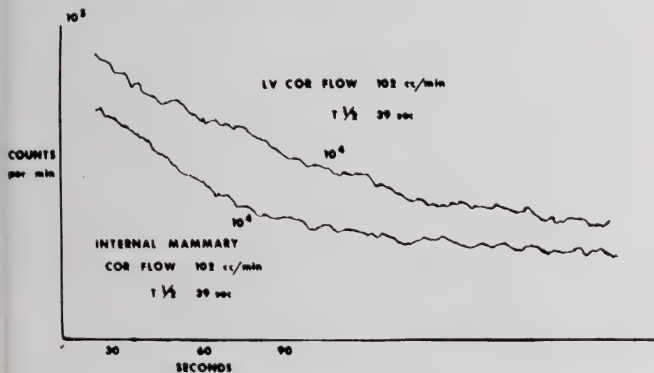


FIG. 15. Krypton 85 disappearance similar whether circulating via implant or coronary artery. (Courtesy of Drs. Gorlin and Taylor)

EFFECT OF INTERNAL MAMMARY PEDICLE IMPLANT ON MYOCARDIAL METABOLISM

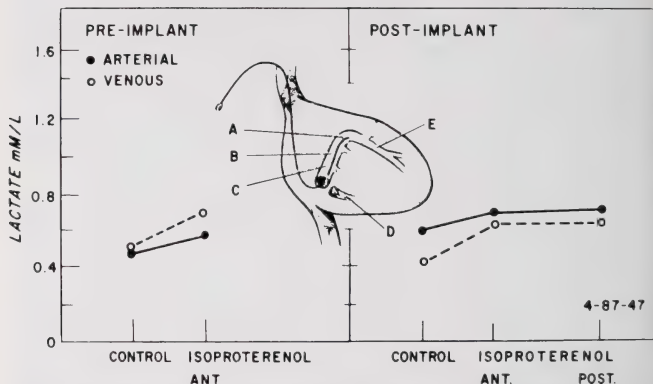


FIG. 16. Typical metabolic findings of lactate production by the myocardium at rest and increased by stress *before* implant and lactate consumption at rest and stress *after* implantation. Anaerobic metabolism (ischemic heart disease) has been reversed to aerobic patterns. (Courtesy of Drs. Gorlin and Taylor)

He has shown by scintillation counting over the precordium and by coronary sinus measurement that the blood delivered by implant and by normal coronaries passes through the myocardium similarly. It does not shunt to a venous pathway directly or into a chamber immediately.

With patency established and the pattern of perfusion demonstrated, you may ask: But does the blood perfuse the heart in sufficient volume to correct ischemic heart disease? Ischemic heart disease is manifested by the *production of lactic acid*. Normally, in the aerobic (non-ischemic) state, lactic acid is consumed by heart muscle, but heart muscle has the capacity to adapt to the ischemic state by anaerobic metabolism—thus, lactogenesis signals ischemia.

Gorlin's studies have shown that some patients suffer the ischemic state constantly; others, only with stress. The patient without ischemia has no need for anaerobic metabolism and therefore does not produce lactic acid. Furthermore, Gorlin has shown with the Brigham implant series that in the areas of successful mammary artery implantation this anaerobic metabolism is *corrected* (Fig. 16).

With our argument defended by *patency, pattern of perfusion, and adequacy of flow* (to the point of correcting ischemic heart disease), we inquire further as to the risk of operation, the relief of pain, and the effect on longevity.

The risk in our first one hundred patients was just over four percent for

unilateral implants and six percent for bilateral implants: respectable and acceptable.

Are patients relieved of pain? Yes. Are they rehabilitated? Yes. Finally, do they live longer? In a personal preliminary report for the purpose of this presentation, Dr. Gorlin tells me that at eighteen months the surgical mortality is balanced by the basic disease mortality in comparable patients without operations. After eighteen months, there have been no deaths in those patients

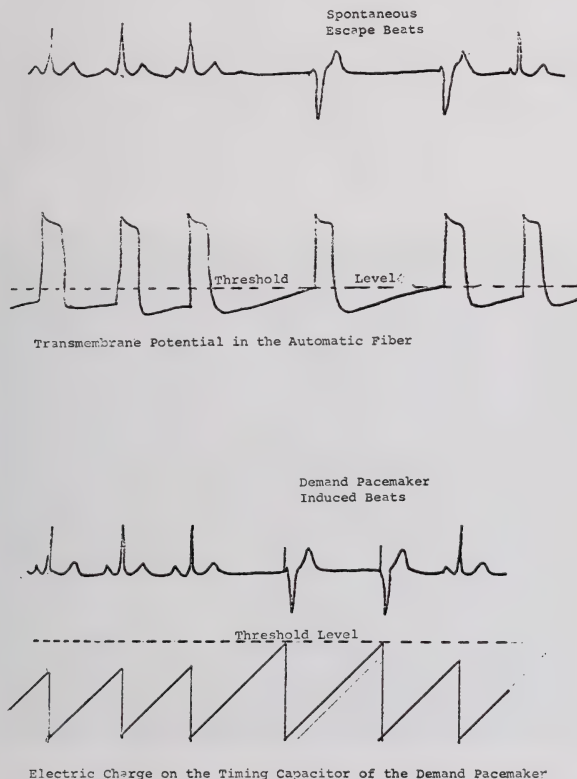


FIG. 17. Comparison of the demand pacemaker action with that of the heart's automatic fibers.

who were operated upon but the standard pattern of fall-out continues in the control patients (not operated upon). Implants are protecting the surgical patients as opposed to their projected course if they had not had surgery.

Having established that an operation can correct ischemic heart disease at an acceptable risk, that it can rehabilitate patients and prolong life, we rest our case.

Those who have residual doubts may take their place with those resisters who want further proof that cigarette smoking and lung cancer are associated.

II. Heart Block and the Demand Pacemaker

All of us congratulate Dr. Paul Zoll for pioneering electrical pacing in heart block. Similarly, we owe a special debt to Sowton who recognized that five times the early mortality (first six months) after pacemaker implantation occurred in patients whose normal mechanisms competed with the implanted mechanical pacemakers. Normally, the energy level from the pacemaker is only a fraction of the threshold for fibrillation. However, a variety of conditions, such as electrolyte imbalance, anoxia, digitalis toxicity, and adrenalin

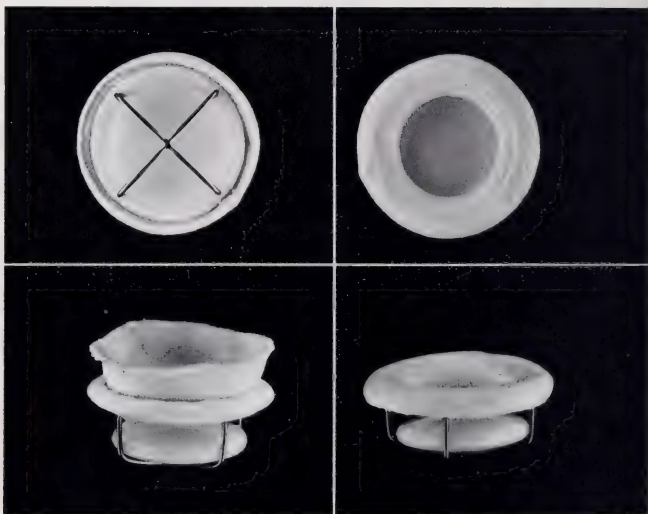
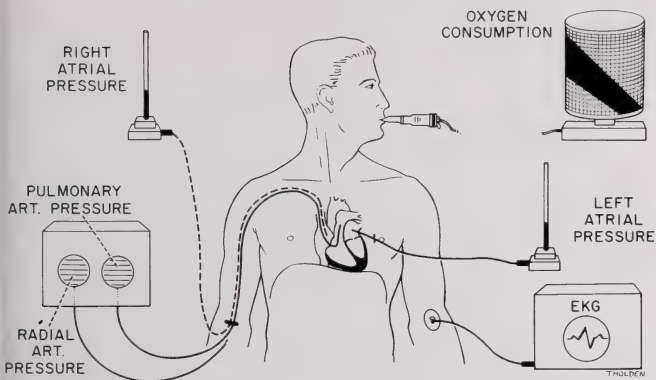


FIG. 18. Author's low profile valve with protective secondary skirt. This valve has a low incidence of emboli and has proven physiologic hemodynamic properties.



MONITORING AFTER VALVE REPLACEMENT

FIG. 19. Monitoring model that allows continuous observation of central arterial, venous, left atrial, and pulmonary artery pressures. Sampling allows frequent Fick or dye dilution determination of cardiac output.

secretion, can decrease the threshold of irritability so that an otherwise safe impulse can fall in the vulnerable period of the "T" interval and cause ventricular fibrillation. It was with this hazard in mind that our colleague, engineer Barouh Berkovits of the American Optical Company, originated the term *Demand Pacemaker* and the device that serves this unique function.

It works precisely like an automatic heart muscle fiber inserted in the myocardium. The power unit (with its capacitor) may be regularly depolarized by the patient's ventricular activity. When there is no such activity in the patient's heart muscle, the demand pacemaker builds up to its threshold potential and stimulates the patient's heart to systolic contraction (Fig. 17).

In this way a physiologically timed impulse is delivered as needed (or on demand) instead of a continuous, unphysiologic pacemaker. It is safe because it cannot cause fibrillation by firing in the vulnerable zone even when the heart is unstable or irritable.

Finally, when the patient supplies his own stimulus, the power drain on the pacemaker power pack is reduced by 90%. Battery survival is therefore longer. If the pacemaker need is continuous, the extra circuit consumes only an additional 10%. Thus, in most patients the demand pacemaker batteries will last longer, be safer, and provide more physiologic cardiac action. There remain very few circumstances in which the demand unit is not preferable. Indeed, many patients even in complete block regain some, if not complete, spontaneous pacing if given the opportunity by the demand pacemaker.

In general, pacemaker insertion should be by the simple intravenous method. The first demand pacemaker was implanted at the Peter Bent Brigham Hospital on August 2, 1966.

III. *The Papillary Muscle Syndrome and Mitral Insufficiency*

Mitral regurgitation is a protean spectrum ranging from various chronic rheumatic forms, some with a herniated valve complex and massively dilated left atrium, to an acute form due to papillary muscle disruption. The latter is generally associated with coronary artery disease. Here the onset is acute, the patient generally a male with myocardial infarction. The heart is small; the atrium is compact (even promptly hypertrophic). The heart is generally in normal sinus rhythm and in addition to the holosystolic murmur in the mitral area, there is a fourth heart sound. If the papillary muscles have sloughed completely, death is prompt. If separation is partial and involves only minor

DISCOID MITRAL VALVE REPLACEMENT PATIENTS WITH SYSTEMIC PULMONARY HYPERTENSION

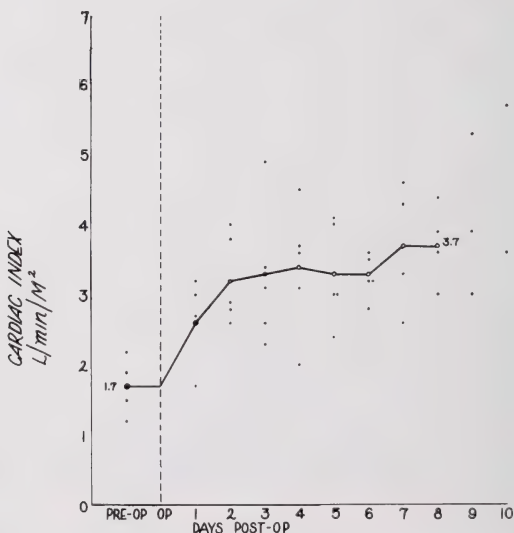


FIG. 20. Five consecutive patients with systemic pulmonary hypertension showed prompt increase in cardiac output after the new lens valve was placed. This is in dramatic contrast to the response after ball valve implantation.

DISCOID MITRAL VALVE REPLACEMENT PATIENTS WITH SYSTEMIC PULMONARY HYPERTENSION

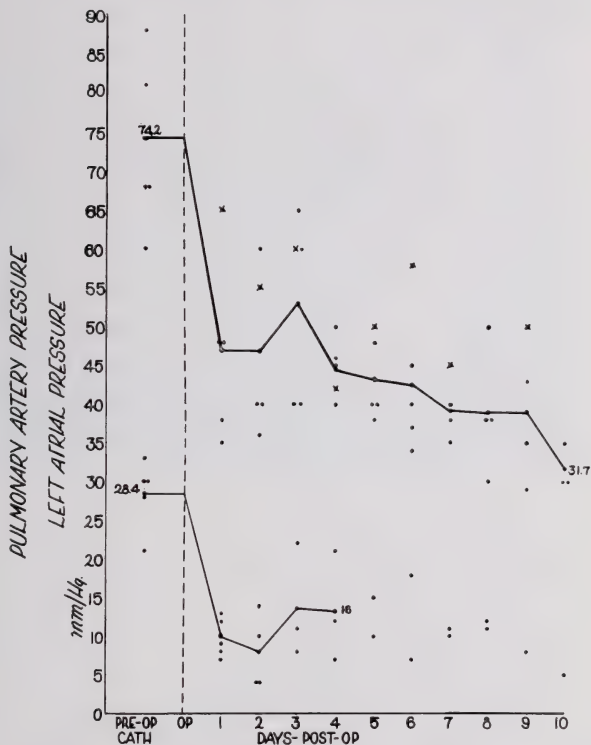


FIG. 21. Prompt fall of pulmonary artery and left atrial pressures occurred in same series of patients with systemic pulmonary hypertension after new mitral valve replacement.

areas of the major leaflet or more extensive portions of the mural leaflet, the patient may survive for weeks or months. To these a prosthetic valve may be life saving. In this connection, valve replacement is stressed. First, because our long-term survival has been conspicuously better with prosthetic

replacement than with valvuloplastic repair; secondly, because there is at least one valve that restores essentially physiologic function with a very low incidence of thrombogenesis. It has also reduced the problem of parabasilar insufficiency (Fig. 18).

In short, this recently recognized syndrome may be corrected with less than 10% mortality, but the surgical decision must be made promptly.

The physiologic evaluation of this valve is consistent with the theme of objectivity and documentation for this Arthur Master Lecture (Figs. 19-22).

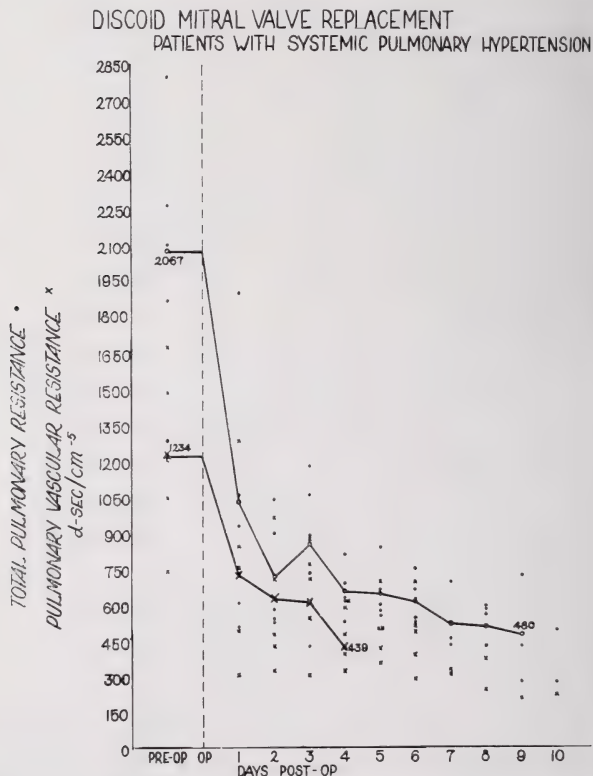


Fig. 22. First demonstration of prompt fall in pulmonary vascular resistance in patients with severe pulmonary hypertension. This is proof that (a) changes are reversible and (b) due in some part to spasm.

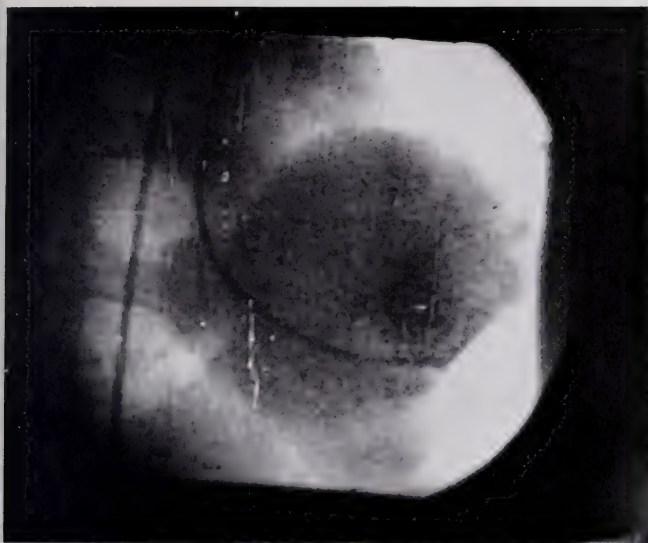


FIG. 23. A frame from the ventriculogram of the large ventricular aneurysm.

These objective studies indicate substantial advantages of this low profile valve over ball valves. These facts support my thesis that:

(1) We have much to offer the patient whose coronary occlusion produces mitral insufficiency and,

(2) There is gratifying objective evidence that this prosthetic mitral valve can function as a normal valve at rest and at exercise (in contrast to the ball valve). Indeed, essentially all ball valves have shown elevated left atrial pressures with exercise. This low profile valve is better (Fig. 18).

IV. *Ventricular Aneurysms*

This end result of coronary artery disease has another special interface with Dr. Master's work. He pioneered documentation of paradoxical myocardial motion in coronary artery disease. In 1939 he photographed the fluoroscopic image by using special lenses.

It is beyond the province of this discussion to dwell on the various degrees of myocardial akinesia, dyskinesia, or paradox. We will generalize at the point of exploring the place for surgical intervention in established left ventricular aneurysms. Such aneurysms can cause disability and death by:

(a) congestive heart failure, 75%

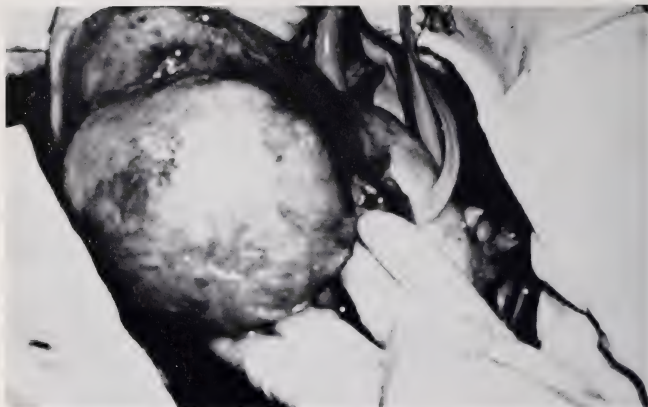


FIG. 24. Ball-like aneurysm in foreground is larger than the heart immediately behind it (frame from colored movie).

(b) coronary insufficiency, 50%

(c) thromboembolism, 10%

Note the absence of rupture. Ventricular aneurysms do not rupture. The reason will become apparent when aneurysmectomy is demonstrated.

Note also the low incidence of thromboembolic phenomena; this can probably be lowered further by anticoagulation. The low incidence of embolism in anticoagulated patients and the response to medical treatment of many patients who have some heart failure, may render surgical intervention unnecessary. To say that the presence of an aneurysm constitutes the indication for surgical intervention is to oversimplify selection.

The one clear indication for surgical intervention now is persistent congestive heart failure in spite of medical treatment.

The place for thromboembolism as an indication for surgical resection, with or without anticoagulation, has yet to be clarified.

The demonstration of the paradox, the potential for congestive heart failure, and the reason for thromboembolism can perhaps best be demonstrated by presenting the resection of what may well be the largest aneurysm ever operated successfully (Figs. 23, 24, 25).*

Clearly progressive failure in spite of medical treatment is the cardinal reason for surgical intervention. Clinical and hemodynamic studies showed

* At this point Dr. Harken showed angiograms of a giant ventricular aneurysm. The colored movies documented its successful surgical resection.



FIG. 25. The massive aneurysm has been resected and the intact mitral valve complex is explored. (frame from movie)

prompt correction of left ventricular failure by resection of this massive aneurysm. The patient has been rehabilitated.

The place of thromboembolism as a surgical indication must still be individualized.

V. Cardiac Assistance by Bypass and Counterpulsation

All who have worked with heart lung machines in open heart surgery have found need for occasional prolongation of bypass to assist the circulation. One needs but to reflect on an extension of this in bypass time, portability with contained energy source, and practicality to appreciate that we are on our way in principle.

That counterpulsation can open dormant intercoronary communications that may help acute and chronic ischemic heart disease seems likely. Even counterpulsation of two hours or fewer can dramatically augment intercoronary communication and increase survival threshold in controlled experimental coronary occlusions in animals (Fig. 26).

Now that critical angiographic and metabolic studies are available to assess the effect of counterpulsation we have a vast area of great promise that must be pursued as a possible palliative treatment for coronary artery disease. Much has been said about counterpulsation and inter-aortic balloons and circulatory assistance for cardiogenic shock. However, to me the conspicuous area of great

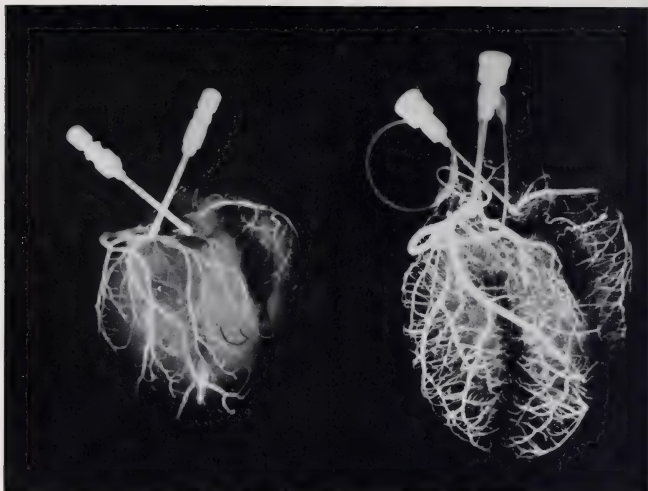


FIG. 26. Comparison of angiograms in animals not counterpulsated with identical microsphere embolization but after two hours of arterio-arterial counterpulsation. Many dormant intercoronary communications are opened promptly.

promise is in acute and chronic ischemic heart disease. The application of this form of assistance is simple and safe. The potential is great.

VI. *Replacement of Hearts*

So much, too much, has been said on radio, television, and in the public press about morals, ethics, doctors playing God, the public playing referee, and so on that I am sickened by this subject. So many committees, commissions, and self-styled authorities have caucused that one is inclined to run away from the subject. After all, "*a camel is a horse designed by a committee.*" However, we are obliged to set down ten commandments:

I. Cardiac transplantation is in the experimental phase. As of this date, it is not a form of therapy.

II. The present knowledge of immune responses and rejection, their control such as by drugs, tissue typing, radiation, antilymphocytic serum, is sophisticated, incomplete, and advancing rapidly. No human heart transplant program should be undertaken without antilymphocytic serum.

III. Definitions of brain death must be clarified and equated with legal death to update our concepts of death, individual rights, and donor selection. This involves anatomic proof of brain destruction.

IV. The possible harvesting of tissues for transplantation in primate centers or the development of mechanical hearts may simplify the whole matter.

V. Clarification of life cycles is needed to select recipients who cannot survive. As examples, Master's prediction of certain death at the third transmural infarction or terminal congestive failure from progressive myocardiopathies; or, local massive obstruction by nonresectable primary malignancy of the myocardium; these and other situations can be explored for recipient selection.

VI. The moral and ethical considerations are far from new to the medical profession. These painfully pedantic and at times pompous discussions have had mixed dividends.

VII. Public display and abuse of public communication media leads to competitive claims and eventually to irresponsible advertising. This constitutes a threat to both the public and patients.

VIII. The conspicuous disadvantage of confused medical and other testimony to the public or in government hearings must be avoided through a definition of policy and principles by responsible agencies or organizations. This involves neither committee case selection nor euthanasia.

IX. Realistic cost accounting must not be ignored in charting the direction and degree of surgical effort. We are now confronted with an obligation to the greatest good to the greatest number with existing facilities. We must equate the massive effort for one unfortunate patient, even with its advantageous learning experience, against the value of similar expenditure for preventive medicine, feeding starving people, birth control, or indeed the price of a bomb! Perhaps it is the price of the bomb that should go on trial first!

X. Surgery is often magnificent palliative treatment but our best efforts are often directed at prevention.

In closing, may we again express the hope that objectivity and facts may control conclusions regarding the selection of patients for surgery. May I extend this to say that in the best tradition of Dr. Arthur Master, such objectivity only underscores the great place of surgery in the field of coronary artery disease.

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Afebrile Bacterial Endocarditis

A Clinical Study of Two Cases

EUGENE M. TEICH, M.D.

Bacterial endocarditis is listed as one of the classic causes of fever of undetermined origin. Osler (1) in one of the early descriptions of this entity stated "endocarditis with fever as its only symptom may be prolonged for weeks or months under many different circumstances." Harrison (2), in his textbook, defines endocarditis as a prolonged, febrile, often fatal disease resulting from bacterial infection of a heart valve, characterized by fever, heart murmur, splenomegaly, embolic phenomena, and bacteremia. Cecil and Loeb (3) emphasize that unexplained fever of more than one week or ten days, in a patient with a heart murmur, should lead to the suspicion of endocarditis and the obtaining of blood cultures. In a discussion of the general symptoms of subacute bacterial endocarditis, Libman and Friedberg (4) note that fever is the constant feature. The course of the fever is variable and may be irregularly remittent or intermittent. It is stated (4) that periods of apyrexia or subfebrile temperatures may be observed for a week or two at a time, especially if uremia develops. In a review of 337 cases of bacterial endocarditis from 1924 to 1963, Rabinovich et al (5) reported that fever was present in every case. Most frequently, it spiked to 103°–104°F in their series, although, all types of fevers were found. Fever was recorded when a rectal temperature of 100.0°F or higher was found before treatment was started. Pyrexia was observed in 24 personally treated cases (100%) by Wedgewood (6). In 4.1% of a series of 148 cases of bacterial endocarditis, reported by Vogler et al (7), there was no record of fever prior to or during hospitalization, with periods of observation lasting up to four months. All of these had either positive blood cultures or autopsy proof of bacterial endocarditis. In Newman's (8) analysis of 52 cases of bacterial endocarditis, fever was present in 85%. In 2 of the 159 patients studied by Cooper et al (9), failure to make the correct diagnosis was due to the absence of significant fever.

The recognition of bacterial endocarditis is the single most important factor influencing survival. The manifestations of this disease may be protean in character and can affect any organ system. No single clinical sign is pathognomonic for this disease. Although fever is the most common clinical finding in bacterial endocarditis, we must be aware of its existence even in the absence of fever. It is the purpose of this communication to report two cases, one with autopsy findings, who had proven endocarditis and who were afebrile during their prolonged period of hospital observation.

From the Department of Medicine, Huntington Hospital, Huntington, N. Y. and the Long Island Jewish Hospital, New Hyde Park, N. Y.

Case Reports

Case 1. B.W., a 51-year-old white pharmacist, was admitted to the Huntington Hospital for rapid, irregular palpitations, associated with weakness, sweating, and fluid retention. The patient had been observed for 1½ years prior to this admission. He had rheumatic heart disease, inactive, with mitral insufficiency, which was hemodynamically significant with left atrial and left ventricular hypertrophy. He previously had one episode of frank congestive cardiac failure which was treated in the hospital with bed rest, rigid salt restriction, and diuretics. At that time, he could not tolerate any oral digitalis preparations and nausea and vomiting developed following minimal doses of digitalis. Administration of digitalis with antiemetics and potassium, separately and in combination, resulted in nausea and emesis.

He had been discharged from the hospital two months prior to this admission, following a left inguinal hernioplasty. At that time, he was given parenteral penicillin, 600,000 units, intramuscularly twice daily, prophylactically, for seven days, and had an uneventful postoperative course. Following discharge, he reported that a rash developed that was thought to be due to a penicillin hypersensitivity. Approximately three weeks prior to admission, a furuncle developed on his left ear. An incision and drainage was performed while he was receiving oral tetracycline therapy.

Several days prior to his last admission, he experienced increasing fluid retention, increasing dyspnea, and orthopnea. Despite the use of salt restriction, oral diuretics, and repeated mercurial diuretics at home, he had rapid, irregular palpitations associated with weakness, sweating, and syncope.

Physical examination revealed a well-developed, middle-aged, white man, acutely and chronically ill. There was evidence of recent weight loss, despite his edema. Neither clubbing nor cyanosis was seen. The cervical veins were distended with fibrillatory waves visible. The lungs were clear and resonant throughout without rales. The heart appeared enlarged to the left and downward. Atrial fibrillation was present with a rapid ventricular response at 130/min, with marked pulse deficit. A systolic thrill was palpated at the apex. There was a prolonged, high-pitched, blowing, Grade 3/6 holosystolic murmur, best appreciated at the apex and radiating into the axilla. No diastolic murmurs were audible. On abdominal examination, no liver or spleen could be palpated, nor was there any hepatic tenderness. Mild ankle edema was present.

PERTINENT LABORATORY DATA: Hemoglobin, 11.3 gm%; total leukocyte count, 19,000 (81% segs, 16% lymphs, 3% monos); blood urea nitrogen, 54 mg%; serum sodium, 125 mEq/L; serum chlorides, serum potassium, carbon dioxide combining power, all within normal range. SCOT 20 units; ASLO titre 166 units; C-reactive protein 2+ positive; serum creatinine 1.75 mg%. Urinalysis on several specimens revealed 2+ albuminuria, 8-10 wbc/phpf, 30-50 rbc/phpf. Total urinary volume for a 24 hour period on three successive days averaged 450 cc; urine sodium 4.8 mEq/24 hours; urine potassium 20 mEq/24 hours. Total eosinophile count 25 cu mm: lupus erythematosus preparations $\times 2$ were negative. Hemoglobins later ranged from 9-10 gm, and last recorded blood urea nitrogen was 90 mg%. Last recorded serum sodium was 145 mEq/L; serum potassium 3.8 mEq/L. 17 ketosteroid excretion was 2.31 mg/24 hours; 11-oxy steroid excretion 1.29 mg/24 hours. The chest x-ray revealed the heart to be increased in its transverse diameter due to moderate left ventricular hypertrophy. There was also evidence of moderate left atrial hypertrophy. An intravenous pyelogram failed to visualize the kidneys. The electrocardiogram revealed atrial fibrillation with a rapid ventricular response. There was evidence of moderate left ventricular hypertrophy. Four blood cultures which were reported on the day of death grew out a luxuriant growth of *Streptococcus viridans* (alpha-hemolytic *Streptococcus*).

HOSPITAL COURSE: At the time of admission, it was felt that this patient had rheumatic heart disease, inactive, with mitral regurgitation and congestive cardiac failure. There was no evidence to support the diagnosis of pulmonary infarction or embolic manifestation. He

was placed at bed rest and was treated with rigid salt restriction and digitalized slowly, with Digoxin which was tolerated at that time. Congestive cardiac failure was no longer a problem after the first three hospital days. The patient's blood urea nitrogen was reported as 54 mg% with urinalyses revealing 2+ albuminuria and multiple wbc and rbc. His serum sodium was reported repeatedly as less than 125 mEq/L. It was felt that this picture was compatible with a salt-losing syndrome, resulting from previous salt restriction, meralluride sodium (Mercurhydrin) and hydrochlorothiazide (Hydrodiuril). An attempt was made to correct this by administering hypertonic saline solution, 10 gm sodium chloride, dissolved in 400 cc of fluid, intravenously slowly. Following this administration, he had a definite improvement with less weakness and lethargy, but still complained of some pains in his legs. Despite this, the blood urea nitrogen remained elevated and went to levels of approximately 85 mg%.

Throughout his hospital course, he remained afebrile. Temperature charts, recording fevers orally and rectally, have been carefully reviewed and reveal no evidence of any fevers recorded above 99.6°F. Figure 1 correlates the mean daily temperatures with other significant clinical events.

On the twentieth hospital day, he complained of weakness, nausea with repeated small emeses, and lethargy. It was noted that his blood urea nitrogen was persistently rising and on that day, without abdominal or back pains, he noted a slight amount of pinkish hematuria. For the first time, physical examination revealed that his spleen was palpable and definite early clubbing had appeared. Five blood cultures were obtained during the next twelve-hour period.

In a patient with known rheumatic mitral valve disease, with symptoms of weakness, weight loss, generalized malaise, myalgia, and lethargy and later developing splenomegaly and clubbing, the diagnosis of bacterial endocarditis seemed quite obvious. Since he had a previous known allergy to penicillin, skin tests were performed with an intradermal test quantity of penicillin G. When this produced no reaction, a cut-down was performed. Prior to the report of his blood cultures, he was started on aqueous crystalline penicillin, 100 million units intravenously daily and Streptomycin, 1 gram intramuscularly two times a day. Despite therapy, on the next day, he had a generalized convulsion and became semistuporous. Despite all emergency measures, the patient expired shortly thereafter, on the 24th day following admission.

POST-MORTEM EXAMINATION: Necropsy revealed bacterial endocarditis with vegetations involving the mitral valve. The mitral valve revealed evidence of previous rheumatic valvular disease. There was a toxic type of splenomegaly noted and the kidneys had the typical "flea-bitten" appearance of embolic glomerulonephritis.

The heart weighed 450 grams. The mitral valve revealed a decreased circumference. There was some calcification at the anulus and also thickening and distortion of the mitral cusps. The atrial surface of the medial mitral cusp displayed a reddish-brown, irregular vegetation, the largest of which measured 0.5 cm in diameter. (See Fig 2 and Fig 3) There was thickening and fusion of the chordae tendinae of the mitral valve. The myocardium had a brownish color throughout. No areas of infarction or scarring were noted. The atrial chambers appeared slightly dilated bilaterally. There was no involvement of the aortic cusps.

The spleen was markedly enlarged and weighed 740 grams. Sections revealed a moderately soft, dark, purplish-red, bulging cut surface, with prominent follicular markings.

The kidneys revealed the renal capsules to be stripped easily, showing a smooth, brownish, external surface with numerous small petechial hemorrhages. Both kidneys had a "flea-bitten" appearance. (See Fig 4) Sections of both kidneys revealed congestive cut surfaces with prominent markings of the cortex and medulla. (See Fig 5 and Fig 6)

The brain weighed 1500 grams and displayed considerable flattening of the cerebral convolutions. Coronal sections of the cerebrum revealed markedly moist cut surfaces. No areas of hemorrhages or softening were noted. Except for the marked edema, the remainder of the sections were unremarkable.

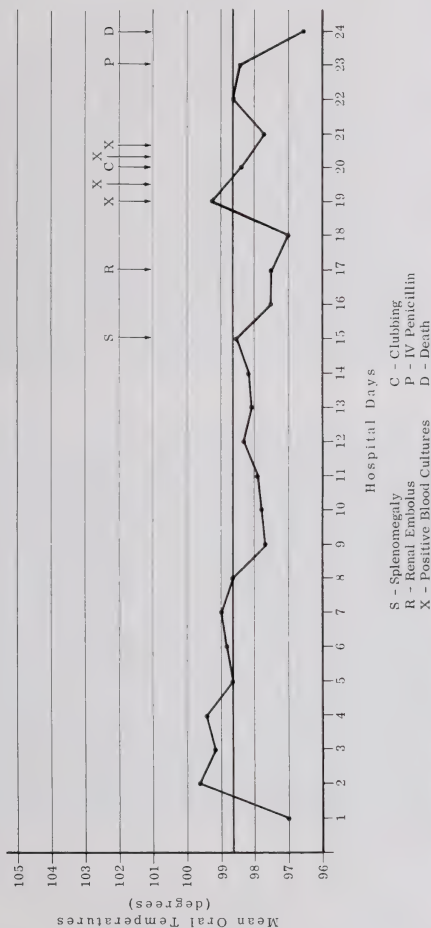


FIG. 1. Case 1 (B.W.) Graphic illustration of mean oral temperature correlated with significant clinical events.

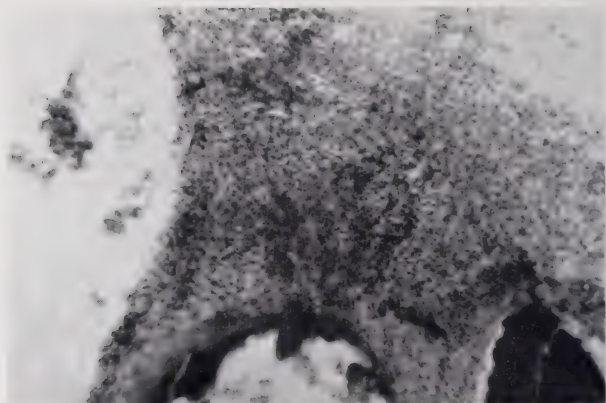


FIG. 2. Section of mitral valve showing focal abscess formation and calcification.

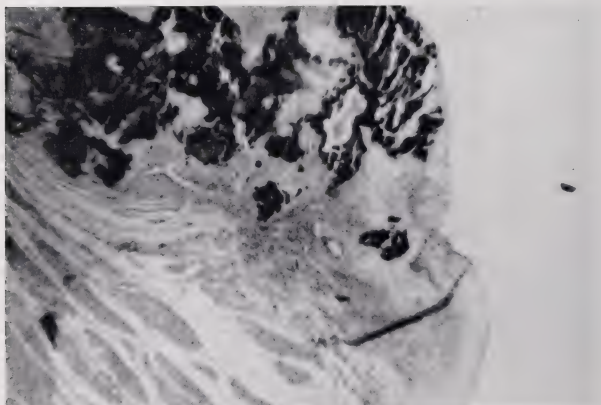


FIG. 3. Section of mitral valve showing extensive necrosis and calcification.

The adrenals were of average size and shape. Sections revealed yellowish cortices and tannish-grey medullae. Microscopic examinations revealed no abnormalities.

Case 2. J.D., a 27-year-old white housewife, was admitted to the Long Island Jewish Hospital because of dysarthria and left-sided paresis for one day.

Approximately six years prior to admission, she was first told that she had a cardiac

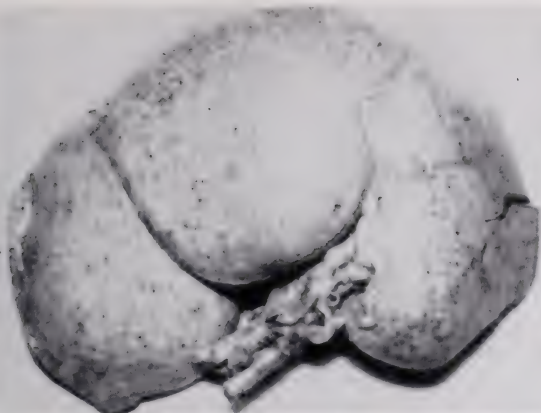


FIG. 4. Kidney showing pale surface with scattered petechial areas, giving "flea-bitten" appearance, characteristic of focal glomerulonephritis.

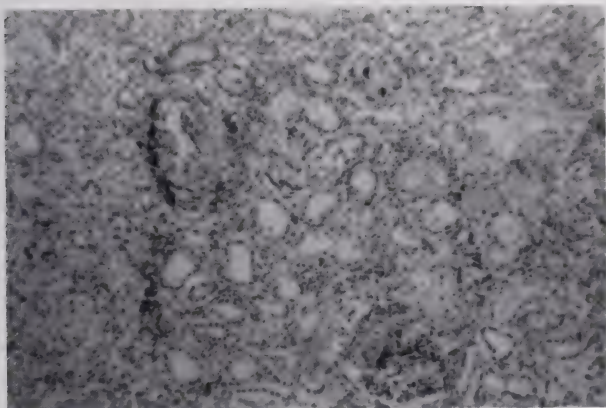


FIG. 5. Section of kidney with two glomeruli showing focal glomerulonephritis.

murmur. There was no previous history of scarlet fever, rheumatic fever, chorea or streptococcal infections. Four months prior to admission, the patient was delivered of a normal baby, after an uncomplicated pregnancy. The only therapy during the pregnancy was oral diuretics. No prophylactic antibiotics were given. Approximately six weeks prior to admission, she first noted increasing fatigue and exercise limitation. She also noticed

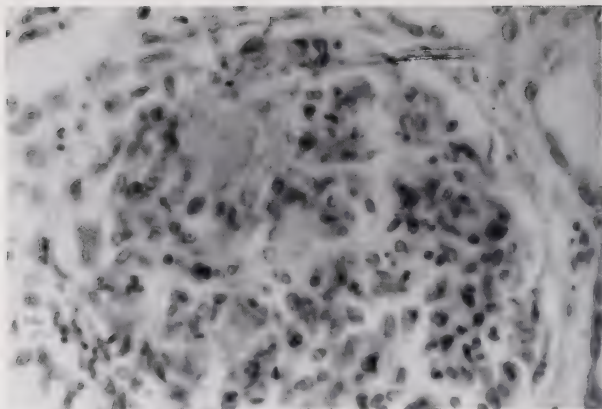


FIG. 6. High power view of glomerulus showing portion of tuft with focal hyaline necrosis or so-called "hyaline thrombi." (Cut scratched in press. Printer)

the onset of "sore, red spots" on the posterior aspect of both legs and ankles, present for approximately four weeks. The patient continued to do her household chores until the evening before admission when she noticed a severe right-sided headache, followed by dysarthria and weakness of her left arm. She later developed a left-sided hemiparesis, involving the upper and lower extremities. There was no history of fever, chills, sweating, anorexia, or weight loss.

Physical examination revealed a well-developed, well-nourished female with obvious difficulty in speaking. Temperature was 98.0° (R); respirations 20/minute; blood pressure 100/60; pulse 100 and regular. The skin revealed several areas of erythema, well-demarcated, measuring approximately one centimeter in diameter, on the pretibial areas of both legs. There was no clubbing, icterus or cyanosis. The lungs were clear and resonant throughout. The heart appeared normal in size, clinically. There was a regular sinus rhythm without any palpable thrills. There was a blowing, prolonged, Grade 3/6 holosystolic murmur, best heard at the apex but transmitted to the left axilla and up the left parasternal line. No liver or spleen could be felt. The extremities were negative. Neurologic examination revealed a left facial paresis as part of a left hemiparesis, upper more than lower. There was a definite paresis of the upward gaze on command and pursuit. There was a mild paresis of left lateral gaze. There was a left Babinski and right equivocal Babinski. Deep tendon reflexes were bilaterally hypoactive. There was no nystagmus or demonstrable visual field defect. No nuchal rigidity was elicited.

PERTINENT LABORATORY DATA: Hemoglobin 12.4 gm%; hematocrit 37%; total leukocyte count 10,700 (80% polys, 18% lymphs, 1% bands, 1% monos). Urinalysis was negative on two separate specimens. Corrected sed. rate 46 mm/hour; blood urea nitrogen 8 mg%; total protein 6.7 gm% with albumin 4.2 gm% and globulin 2.5 gm%; C-reactive protein 1+. Cerebrospinal fluid cell count was 5 WBCs and protein 17 mg%. Spinal fluid culture revealed no organisms. Lupus erythematosus preparations $\times 3$ were negative. Serum VDRL was negative. Urine for porphyrins was negative. X-rays of the skull were negative. X-rays of the chest revealed some straightening of the left cardiac border, but no distinct chamber enlargement was identified. The electrocardiogram revealed a regular sinus rhythm

with no abnormalities. The electroencephalogram revealed an abnormal record, showing focal dysfunction at the right posterior temporal area. Four out of six blood cultures showed anaerobic *Streptococcus* which was sensitive to penicillin, streptomycin, oxytetracycline, chloramphenicol, nitrofurantoin, novobiocin, neomycin, erythromycin, oleandomycin, and polymyxin B. A vaginal culture grew out anaerobic *Streptococcus*, similar to that isolated from the blood cultures. Blood cultures, taken after therapy was begun, were sterile.

HOSPITAL COURSE: The highest recorded temperature during the first six days of hospitalization was 99.6°F rectally. In a patient with known rheumatic mitral valvular disease, and neurologic findings in keeping with a right-sided cerebral embolus, the diagnosis of bacterial endocarditis was entertained on admission. The patient also gave a history of penicillin hypersensitivity with an urticarial reaction following penicillin administration several years ago. In view of this history, on the seventh hospital day, the patient was started on Erythromycin, 1 gram, orally, four times a day. On the next day, definite splinter hemorrhages were noted in the nail-beds. Because of the gravity of the situation, the Erythromycin was discontinued after one day, and the patient was started on aqueous crystalline penicillin G, 10 million units intravenously daily, and Streptomycin, 1 gram, intramuscularly, twice a day. Streptomycin was continued for three weeks and penicillin was continued for a full six-week course. The patient did develop a rash which was probably related to penicillin hypersensitivity and this responded to Chlortrimeton. The patient remained afebrile throughout her hospital stay, except for one temperature rise to 101.0°F on the thirty-fourth hospital day, which was probably related to a phlebitis of the left arm, at the site of intravenous infusion. Following this, the patient continued to improve gradually, and was ambulatory. The left-sided paresis slowly responded and returned to almost normal function. There was slight weakness in some of the fine motions of the left hand and slight drooping of the left angle of the mouth. Gaze returned completely to normal. After six weeks of penicillin therapy, the patient was discharged and has remained well since that time.

Discussion

The clinical manifestations of bacterial endocarditis have conveniently been placed in three general categories of symptoms by Tompsett (10). The first are the systemic manifestations of infection; second, the manifestations of embolization; third, the manifestations of heart disease, itself. The major systemic sign of infection in bacterial endocarditis is fever. This fever may be continuous, remittent, intermittent or completely irregular. As a rule, the daily temperature peaks range between 101°–103°F. Periods of subfebrile temperature for weeks at a time, are occasionally observed in the subacute cases. Friedberg (11) has stated that the diagnosis of subacute endocarditis should be assumed as most probable, whenever a patient with an organic cardiac murmur experiences fever, without apparent cause, for more than one week. Experience has taught that regardless of theoretical possibilities, the diagnosis of bacterial endocarditis based on the above criteria is virtually always correct, if the fever is unequivocal (101.0°F or higher).

The clinical picture of bacterial endocarditis as it occurs in the elderly is much more often atypical than in younger patients (12). In this regard, the normally low body temperatures of an elderly person may result in confusion. The patient reported may actually have some "clinical fever" with a temperature of 99.0°F, if his normal body temperature was 97°–98.0°F. In the elderly patient, the chief obstacle to an early diagnosis of the disease is the common occurrence of a variety of pathologic processes in the same

person and the difficulty in distinguishing the clinically more significant findings.

There are five distinct clinical situations in bacterial endocarditis where the patient may, for at least short periods of time, be afebrile. The first of these is in patients who have received previous antimicrobial therapy in suboptimal doses. These drugs may temporarily arrest the bacteremia but be inadequate to eradicate the underlying valvular vegetation. The second condition occurs after massive intracerebral or subarachnoid bleeding due to embolism or rupture of a mycotic aneurysm. (Case 2 of this study may be apyrexia due to mycotic embolism of the central nervous system.) The third situation is severe congestive cardiac failure. The fourth is uremia, whether it be due to focal embolic glomerulonephritis, diffuse glomerulonephritis or multiple renal septic infarcts. (Case 1 would fit into this category.) The fifth is in the elderly age group, in whom the immunochemical response to bacteremia may be so impaired that clinical temperature elevations do not occur.

The classic criteria for the diagnosis of bacterial endocarditis, namely, unexplained fever and organic cardiac murmur, are well recognized. It is well known that a small percentage of patients with bacterial endocarditis do not have an organic cardiac murmur, especially elderly patients and those with endocarditis due to more virulent organisms. Now, it seems appropriate to add that any patient with an organic cardiac murmur, in the absence of fever, may have bacterial endocarditis. The findings of organic cardiac disease when coupled with anemia, weakness, weight loss, generalized malaise, splenomegaly, petechiae, clubbing, microscopic hematuria or an embolic phenomenon should always prompt the clinician to obtain blood cultures and initiate therapy. In order to avoid missing the diagnosis of bacterial endocarditis on any medical service, blood cultures should be obtained on all cardiac patients with any unexplained findings.

POST-PARTUM ENDOCARDITIS

DeLee and Greenhill (13) list that puerperal infections are caused by *Streptococcus viridans* and hemolytic and nonhemolytic *Streptococci* (aerobic, anaerobic, facultative, obligate). It is stated that it is rare to find one of these organisms as a sole cause of the disease. In a control series (14) from 30 of the 32 uterine cultures in untreated patients, various bacteria were isolated, predominantly anaerobic *Streptococci* and *Bacteroides*. The incidence of positive blood cultures following parturition is difficult to estimate. Burwell and Metcalf (15) obtained no positive cultures in 17 patients during and after termination of labor. Blood cultures obtained by Redleaf and Fadell (16) were positive after delivery of the placenta in 4% (4/101) and were positive in 11% (11/101) in the first postpartum day. A review of the world literature to 1953 (17) revealed only 35 reported cases of subacute bacterial endocarditis in pregnancy. The calculated incidence was approximately 0.02% of pregnant women.

When bacterial endocarditis occurred during pregnancy and an organism

was isolated in the blood stream, it was invariably *Streptococcus viridans*. In contrast, it was found (18) that when the disease developed during the postpartum period, the predominance of organisms was that other than *Streptococcus viridans*. The outstanding feature of the analysis of 8 cases by Lein and Stander (18) is that none of the 7 patients with histories and physical findings indicative of heart disease, received prophylactic antibiotics.

Antimicrobial prophylaxis does not appear warranted during the course of uncomplicated pregnancy in patients with predisposing cardiovascular disease. The pregnant cardiac patient should be observed frequently for any intercurrent infections, which should be treated vigorously. At the onset of labor, these patients should receive aqueous or procaine penicillin 1.2 million units intramuscularly, combined with Streptomycin 1 gram intramuscularly, prophylactically, followed by half this dose every twelve hours while labor progresses. This program should be continued through the second postpartum day. For patients with a history of hypersensitivity to Penicillin or Streptomycin, Tetracycline in therapeutic doses should be given instead of the Penicillin-Streptomycin regimen.

Case 2 is a patient with known rheumatic valvular disease who received no antibiotic prophylaxis during pregnancy and the postpartum period. The organism isolated from the blood cultures was an anaerobic *Streptococcus*, which also grew luxuriantly from a vaginal smear. It seems most likely that the endocarditis followed the transient bacteremia, which occurred during labor or immediately postpartum.

PROPHYLAXIS

Prophylactic antibiotic therapy is indicated in anyone with known cardiac disease who is undergoing any dental procedure or minor surgical procedure. The program to be instituted in women who are pregnant, during labor and in the immediate postpartum period, has already been outlined.

All patients with cardiovascular disease predisposed to bacterial endocarditis who are involved in trauma to the genital or urinary tract should receive antibiotic therapy directed at the *Enterococcus* just prior to and after the procedure. The accepted regimen consists of Procaine Penicillin 1.2 million units intramuscularly and Streptomycin 1 gram intramuscularly about one hour prior to the procedure, with repetition at twelve-hour intervals for a total of three days. Although gram-negative enteric bacilli are responsible for the vast majority of instances of bacteremia after urinary tract manipulation, these organisms are distinctly unusual as causes of bacterial endocarditis. Therefore, in these procedures, prophylaxis must be directed at the *Enterococcus* (19).

To date, no proof exists that prophylaxis with antibiotics is effective in preventing bacterial endocarditis in someone undergoing traumatic procedures associated with transient bacteremia. However, antimicrobial prophylaxis appears to be a reasonable approach and the consensus of expert opinion favors the use of antibiotics in this situation. In endocarditis associated with intra-

cardiac prosthesis (20, 21), the establishment of an augmented antibiotic program to include the preoperative administration of Procaine Penicillin, Streptomycin and Methicillin, followed by oral Sodium Oxacillin for a period of two to three months, has resulted in a sharp decline in the incidence of Staphylococcal endocarditis. In clinical situations other than cardiac surgery with intracardiac prosthesis, the prolonged administration of antibiotics after a procedure is unjustified.

Summary

Two patients, one with detailed postmortem findings, are presented with proven bacterial endocarditis, who were afebrile throughout their hospital course. Although fever is the major systemic sign of infection in bacterial endocarditis, its absence should not mislead the clinician to discard this diagnosis. Five distinct clinical situations in bacterial endocarditis may be associated with apyrexia: (1) prior administration of antimicrobial drugs; (2) massive intracerebral or subarachnoid bleeding due to embolism or ruptured mycotic aneurysm; (3) severe congestive cardiac failure; (4) uremia; and (5) elderly individuals who may manifest many atypical features.

Since prognosis is directly related to the prompt institution of antibiotic therapy, a high index of suspicion must be maintained. Blood cultures should be obtained on all patients with organic cardiac murmurs with or without significant fever, who display any unexplained findings.

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Eosinophilic Meningitis: Report of Two Unusual Cases

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Meningitis associated with a primarily eosinophilic pleocytosis has recently received increased attention, usually implicating larval infection by the rat lungworm, *Angiostrongylus cantonensis* (1-3).

Reports unassociated with parasitic infections are infrequent (4). A single case report of bacterial meningitis (pneumococcal) associated with eosinophilic pleocytosis was reported in 1964 (5). Numerous cases of apparent hypersensitivity affecting the cerebrospinal fluid have been reported secondary to spinal anesthesia (6-8), pantopaque myelography (9-11) and oral ingestion of sulfonamides (12-13), but none of these instances was associated with an eosinophilic pleocytosis. The present report describes two cases of eosinophilic cerebrospinal fluid pleocytosis apparently unassociated with parasites.

Case Reports

Case I. In 1954, a 34-year-old female was found to have hemolytic anemia and the diagnosis of systemic lupus erythematosus (SLE) was made. She was treated with oral Prednisone®. Her first Mount Sinai Hospital (MSH) admission was in 1959, when an increased rate of hemolysis was noted. At that time, there were repeated positive SLE preparations.

Neurologic involvement was first noted in 1961. The patient complained of burning pain in the left extremities and later experienced episodic cramping of the right lower extremity. There was blurred vision in the right eye and she was readmitted to MSH on 7/25/61. Examination at that time revealed a broad-based gait and she tended to favor the right lower extremity when walking. There were obvious episodes of palpable cramping of the right extremities associated with simultaneous pain in the left thigh, groin, and abdomen. The deep tendon reflexes were increased in the right lower extremity and there was a right Chaddock sign. Pin and temperature sensibilities were reduced to absent from the midthoracic region distally through all sacral levels. There was reduced adaptation time and prolonged after-sensation to pinprick stimulation in the left arm. In the right eye, there was a temporal scotoma and the disc margins were slightly blurred. There was hyperemia and exudate in the right optic papilla. Vision in the left eye was intact. Examination of the left fundus was normal.

Throughout the hospital course, there were frequent episodes of "clawing" of the right hand and foot and simultaneous stiffening and pain of the left extremities. Bilateral Babinski signs developed. There was diminished pin, touch, temperature, and vibratory sensibilities from the level of the Th-4,

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distally on the left side. It was felt that the multiplicity of lesions (cervical spinal cord and right optic nerve) suggested an independent demyelinating disease, i.e. multiple sclerosis. That this process was secondary to SLE, could not be excluded.

Initial laboratory findings included positive Coombs tests, a peripheral white blood count (WBC) of 6300 (no eosinophiles) and hemoglobin of 11.9 grams. The remaining laboratory results, including urinalysis, liver function tests, serum electrolytes, blood urea nitrogen, fasting blood sugar and serum calcium and phosphorous were normal. The initial lumbar puncture (LP) performed on the evening of admission, revealed an initial pressure (IP) of 80 mm of water. The cerebrospinal fluid (CSF) was clear and colorless. Protein and sugar levels were normal. There were 9 white cells/mm³ (8 lymphocytes and 1 polymorphonuclear). The culture produced no growth. She was given 40 mg of intrathecal Depomedrol® at that time.

On the afternoon of 7/26 (the next day), she complained of headache and pain in the back, for which she received oral Demerol®. She was later found thrashing about in bed, disoriented and confused. She was unaware of her location and was incontinent of urine. The oral temperature was 100.2°F. Her pulse rate was 80/min and the blood pressure 100/60 mm Hg. A second LP at that time revealed opalescent fluid in all tubes. There were 2800 WBC/mm³, all eosinophiles. A gram stain was negative. There was 468 mg% of protein and 12 mg% of sugar. Of two culture specimens, the first grew "type 25 pneumococcus" and the second was sterile (reported on 7/28).

By the morning of 7/27, she was still confused and disoriented and appeared to be in pain. There was nuchal rigidity and the oral temperature was 101.2°F. A third LP again revealed opalescent CSF and contained 1,650 white blood cells/mm³ with "numerous eosinophiles." The opening pressure was 150 mm of water. The protein and sugar specimens were lost, but the cultures were sterile. The peripheral WBC was 21,450/mm³ with a shift to the left, but no eosinophiles.

By the evening of 7/28, she was much improved. She was oriented, alert, and complained of headache, but was amnesic for the previous 36 hours. There was still slight nuchal rigidity and eye ball tenderness, but she was able to sit up in bed and read. At this time, the positive culture report (pneumococcus) was obtained and the patient received 20 million units of intravenous penicillin-G daily. A fourth spinal tap (7/28) showed an IP of 140 mm of water. The fluid was slightly cloudy and contained 1300 white cells/mm³ of which 1030 were polymorphonuclear cells. Gram stain and subsequent cultures were negative. She became afebrile and antibiotic therapy was discontinued after three days. During this period, the neck stiffness and headache had subsided.

Subsequent follow-up to January, 1968 has shown some fluctuation in her illness. There was continuation of the spasms of the left leg, a relative sensory level for pinprick and temperature (with its upper level at T10-11) sensibilities and a mild paraparesis. The scotoma in the right eye persisted and both optic discs were pale. Lumbar puncture at that time (1968) showed clear and

colorless fluid with 28 mg% of protein and 108 mg% of sugar. There was a single lymphocyte. She received a series of six injections of intrathecal Depomedrol® (40 mg each) at three day intervals. There was no adverse reaction or increase in the CSF cell count.

Case II. A 51-year-old man was admitted to MSH (11/11/65) complaining of pain in the posterior aspect of the left shoulder of three weeks' duration.

The pain worsened with head extension and radiated posteriorly into the arm and forearm to the dorsum of the hand and the medial four fingers. Numbness and paresthesias were present in the volar aspect of the left index finger and the dorsal forearm. He had noted weakness in the hand and forearm which had begun to interfere with his work (making costume jewelry).

On examination, he tended to keep his head tilted to the left. There was marked weakness of left arm flexion, wrist extension and flexion, hand grip and thumb abduction and extension. There was diminished pinprick and touch sensibility over the volar aspect of the left index finger and dorsum of the forearm. The left triceps reflex was depressed when compared with the right.

General laboratory results were normal. The cerebrospinal fluid was clear and colorless and the protein was 43 mg%. On 11/15/65, a cervical myelogram was performed with 18 cc of pantopaque. A filling defect was found at the left C6-7 interspace which was interpreted as disc herniation. At completion of the myelogram, 12 cc of pantopaque were removed and he was given 40 mg of intrathecal Depomedrol® (14-15). A cervical collar was prescribed and he improved progressively until discharge on 11/30/65.

He was readmitted the next day. He had awakened with pain in the right lateral thigh and midlow back. This was later followed by a headache which was made worse by coughing. He walked with a limp. By midafternoon, his oral temperature was 101.2°F.

Examination at admission revealed slight stiffness of the neck and pain in the midlumbosacral region where there was percussion tenderness. Strength in the left arm and wrist was only slightly less than the right. Hand grip was normal and the left triceps reflex was still diminished. There was pain referred to the right hip on straight leg raising to 30° on the right and to 60° on the left.

The peripheral WBC was 6500 with a shift to the left (6% were eosinophiles). The urine contained 2+ protein. Lower spine x-rays revealed dispersed pantopaque into the root sleeves bilaterally. The remaining laboratory values were normal. LP showed uniformly cloudy CSF with 1400 white cells/mm³. Forty-four percent were eosinophiles. The protein was 79 mg% and the sugar, 68 mg%. Gram stain and subsequent cultures were negative.

He was immediately begun on daily intravenous penicillin-G (40 million units), chloramphenicol (2 grams) and sulfisoxazole (6 grams subsequently reduced to 4 grams). The chloramphenicol was discontinued after 5 days and the remaining drugs, after 11 days. Throughout the period of therapy, the systemic eosinophile count varied from a high of 18% (8th hospital day) to a low of 4% (12th hospital day) as shown in Table 1. Serial LP's at 3 day inter-

TABLE I
Serial Values of Cerebrospinal Fluid and Blood

Hospital Day	Cerebrospinal Fluid			Blood		
	WBC	% Eos.	Protein	Sugar	WBC	% Eos.
1	1400	44	79	68	9,500	6
6	642	30	193	72	7,850	12
8	—	—	—	—	6,800	18
12(1)*	952	31	248	36	7,100	4
16(2)	214	—	86	50	10,000	4
19(3)	5	—	76	42	12,000	—

Serial cell count, sugar and protein values of cerebrospinal fluid and blood. Note the rapid drop in spinal fluid pleocytosis and protein content following the initiation of intrathecal Depomedrol.

* Initiation of intrathecal Depomedrol[®] therapy (total of 3 injections), total 120 mg.

vals revealed a progressive rise in protein to 248 mg% by the 11th day. CSF sugar levels were as low as 36 mg% (simultaneous blood sugar was not obtained).

Throughout the hospital course, there was a progressive decrease in pain and discomfort. He became afebrile after the first hospital day and remained so thereafter. Neck stiffness was much less by the 6th hospital day when ambulation was begun. By the 12th hospital day, he had only a mild headache and minimum percussion tenderness in the lower back. He was asymptomatic by the 19th hospital day when there was no detectable weakness in any extremity. The left triceps reflex remained depressed. There was no detectable sensory deficit when he was discharged on 12/20/65.

Discussion

In Case I, it is difficult to be sure of the etiology, but certainly it is very suggestive of pneumococcal meningitis. The presence of a positive culture, a low cerebrospinal fluid sugar and a good response coincident with antibiotic therapy (though not optimal in time) all strongly suggest this diagnosis. No parasites were found in the blood, urine or CSF. There has been only one other report of eosinophilic pleocytosis secondary to pneumococcal meningitis (5). However, even this case report includes a number of reservations. The patient was seen in French Indonesia which appears to be an endemic area for the syndrome of eosinophilic meningitis secondary to parasitic invasion of the nervous system. He was also noted to have a positive skin test indicating prior exposure and almost assuredly, infection, with the rat lungworm—*Angiostrongylus cantonensis*. Further, the authors reported that many specimens of cerebrospinal fluid taken from patients in this region without evidence of central nervous system illness, show an eosinophilic pleocytosis. Indeed, the authors mention the possibility of the patient having two unrelated illnesses.

A less probable etiologic relationship may have been the prior intrathecal

injection of Depomedrol®. However, this is unlikely in view of the 9 white cells present in the CSF in the initial LP. In addition, she received six subsequent intrathecal Depomedrol® injections in 1968 without adverse effect.

Despite numerous case reports of iatrogenic meningitis, there were no cases with eosinophiles in the CSF (16-18). The rarity of eosinophilic pleocytosis secondary to bacterial meningitis is exemplified by its failure to occur in two extensive reviews of the subject, involving over four hundred patients (19-20). The present patient is thus unique in responding to pneumococcal meningitis with an eosinophilic pleocytosis. The relationship of this response to the lupus erythematosus, itself a disease of altered immune response, is intriguing but not revealing.

In Case II, there is little to implicate an infectious relationship, but much to indicate an allergic reaction to pantopaque. The 16-day delay from the day of myelography to the development of symptoms has been reported in the past (9, 21). However, the quiescent period could also be attributed to a delayed antibody response due to the prompt instillation of intrathecal Depomedrol®. That the pleocytosis did not respond to ten days of intensive antibiotic therapy, but did respond quickly to the further injection of intrathecal Depomedrol®, strongly suggests a hypersensitivity reaction to the previous injection of pantopaque. All blood and CSF cultures were negative and no parasites were found in the blood, urine or CSF. The prompt response of the CSF pleocytosis (Case II) to intrathecal Depomedrol® suggests its possible efficacy in hypersensitivity reactions of the spinal meninges. To date, no untoward reactions or further symptoms referable to the meninges have occurred in either of the presented case reports.

Previous case reports and reviews of naturally occurring bacterial meningitis (19, 20), bacterial meningitis complicating neurologic manipulation (16-18), apparent hypersensitivity meningitis associated with systemic drug (12, 13), chemical meningitis (6-8, 22) or meningeal complications of myelography (9-11, 21) all fail to show a single case of eosinophilic pleocytosis. The most common etiologic relationship to eosinophilic meningitis noted in the literature is parasitic invasion of the central nervous system, usually associated with cysticercosis or echinococcosis (1, 23, 24).

More recently, an etiologic relationship has been suggested with the rat lungworm, *Angiostrongylus cantonensis* (1, 25-28). A similar syndrome (eosinophilic pleocytosis) in cattle has been associated with lead intoxication, but apparently has not been seen in man (29). There were no such relationships suggested in the cases presented in this report.

Conclusions

Two cases of meningitis associated with eosinophilic CSF pleocytosis are presented. Case No. I appears to be the second reported instance of an eosinophilic reaction associated with pneumococcal invasion of the cerebrospinal fluid. Case No. II is apparently the first reported instance of eosinophilic pleocytosis following pantopaque myelography. The rapid response of the sec-

and case to intrathecal steroid therapy suggests its possible efficacy in such instances.

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Diabetic Neuropathic Ulcer

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Foot lesions in diabetes have usually been attributed to the presence of occlusive peripheral vascular disease which tends to occur earlier, more frequently, and with increased severity in diabetes. Insufficient attention has been paid to diabetic neuropathy as a causative factor. Because of the need for proper recognition, and the response to appropriate therapy, a study of neuropathic ulcers in diabetes including its clinical representations and treatment was undertaken.

The term "neuropathic ulcer" is used for a special type of lesion that occurs in any neuropathic foot whatever the cause—i.e. diabetes, tabes, syringomyelia, hereditary sensory syndrome, or leprosy. Synonyms include: mal perforans; plantar ulcer; trophic ulcer; perforating ulcer; or pressure ulcer. Anesthesia (either peripheral or central in origin) is the common denominator in the pathogenesis by virtue of the fact that the foot loses its warning mechanism and the patient is unaware of where and how he places his foot, nor does he perceive trauma. In addition to impaired sensory perception, the application of an abnormally increased pressure to limited surface areas is required. Thus, the lesion occurs only when walking is possible and, conversely, does not occur in the absence of locomotion. Hence, it is uncommon in such disabling conditions as transverse myelitis where the patient is so often bedridden.

Clinical Data

Thirty-six patients with neuropathic ulcerations comprised the basis for this clinical study. Many of the patients had more than one ulcer, though not necessarily at the same time; thus there were 52 lesions in all.

1. *Sex and age.* Of the 36 cases with diabetic neuropathic ulcers, 23 were males and 13 were females. This male predominance has been recorded previously in diabetes (1) and leprosy (2). The youngest person in our group was 32 years of age and the oldest was 75. Sixteen were below the age of 50, and 20—slightly more than half—were more than 50 years of age.

2. *Duration of diabetes.* Sixteen patients had diabetes less than ten years and the remaining 20 had diabetes for more than ten years. Four of our patients experienced the neuropathic ulcer as the initial clinical manifestation of the disease. The recognition of this as a diabetic phenomenon served as a clue to the correct diagnosis (3).

3. *Precipitating factors of onset.* Four patients recalled a distinct injury such as stepping on a sharp edge of rock or a piece of glass; three related the ulcer to shoe trauma; four noted the onset of the ulcer after shaving a callus; and one noted it after a burn following exposure to the heat of an electric cradle.

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4. *Location of ulcer.* The 52 ulcerations in these 36 patients were distributed equally between right and left feet. Nineteen lesions involved the area over the head of the first metatarsal and 25 involved the area overlying the second and third metatarsal heads. One was located at the base of the foot following trans-metatarsal procedure and two were located on the lateral side of the midfoot secondary to Charcot joints and abnormal pressure points.

5. *Bacteriology.* Cultures were made of 32 ulcers. *Staphylococcus aureus*-coagulase, mannitol, and hemolyticus positive- was present in 24 cases; beta hemolytic streptococcus was present in six cases and each time in conjunction with *staphylococcus aureus*. *Staphylococcus albus* hemolyticus was present in two instances, pyocyanus five times, *B. proteus* six times, non-hemolytic streptococcus twice and *Aerobacter aerogenes* six times. More than one organism was frequently encountered in each case.

6. *Peripheral vascular status.* In 32 of the 36 patients, all pulsations in the lower extremities were readily palpable. In four cases the dorsalis pedis artery was not palpable and in two of these the posterior tibial pulses were absent; nevertheless, the feet were warm, thermocouple readings were normal, and there was no clinical evidence of vascular insufficiency. Normal venous emptying on leg elevation and warm feet were uniformly encountered. The lesion clearly is not related to inadequate blood supply.

7. *X-ray findings.* Although it might be anticipated that severe bone changes would be encountered in conjunction with peripheral neuropathy and ulceration, this finding was quite inconspicuous in our series and as previously reported (4). Of the 36 patients, only four showed a mild to moderate degree of osteoporosis; there was one case of suspected osteomyelitis and three instances of Charcot arthropathy. In fifteen patients there were evidences of vascular calcification most often of the posterior tibial, the dorsalis pedis, or the interdigital arteries. It was obvious that the state of the circulation in terms of roentgenographic vascular calcification could not be determined.

8. *Control.* Three patients were controlled with diet alone. Eight were controlled with diet plus oral hypoglycemic agents. The remaining 25 required insulin in dosage ranging from 10 to 100 units. Although admittedly difficult to evaluate the degree of control, most of our patients would be considered to be at least under fair and many under good control. Poor control over a prolonged period of time occurred infrequently in this series. None of these patients had any episodes of diabetic ketoacidosis and the incidence of hypoglycemic reactions was low.

9. *Laboratory findings.* Blood cholesterol studies were done in 29 of the 36 patients and of these only five exceeded 250 mg%, the highest being 298 mg%. Of the 36 patients, 28 had normal blood pressure. Eight had hypertension, the highest being 190 mm mercury systolic over 100 mm mercury diastolic. Fifteen patients had albuminuria ranging from a faint trace to 2 plus; the other 21 had neither albuminuria nor clinical suggestion of diabetic nephropathy.

10. *Associated clinical conditions.* Twenty-four of the patients had retinopathy; six of these had very severe involvement including detached retina. Four had Charcot arthropathy, three had diabetic enteropathy, three had neurogenic vesical dysfunction and eight were impotent. Fifteen had clinical manifestations

of diabetic nephrosclerosis and one had papillary necrosis demonstrated by x-ray and later by autopsy. Four of the patients had congestive heart failure. It would seem, therefore, that the presence of a neurotrophic ulcer in diabetes usually indicates the existence of other specific degenerative complications.

11. *Neurologic disturbances.* Every patient had unmistakable evidences of peripheral neuropathy. All had impairment of pain; most had involvement of touch, temperature, pinprick, and position sense. Trophic changes of the skin and toenails were common. Diminution to absence of sensation in stocking and often in glove distribution was the rule. All 36 had absent ankle jerks, and knee jerks were absent in 18 patients. Subjectively, most of the patients had a preceding history of pain in the feet, sole, and toes and all complained of or recalled paresthesias. Patients' descriptive statements include: "my feet feel as though they don't belong to me"; "my feet feel dead"; "I'm walking on pillows"; and "I'm walking on clouds." Atrophy of interosseous muscles of the feet were present and not infrequently accompanied by comparable wasting in the hands and upper extremities. Lumbar puncture performed in 16 patients revealed normal spinal fluid protein in five and an elevation ranging from 50 to 78 mg % in 11. All had negative spinal fluid serology.

Clinical Observations

Neurogenic ulcers are characteristically painless, as evidenced by the fact that a serous discharge on the sock or stocking is often the first sign of the lesion's presence. The basis of sensory impairment is confirmed by the development of similar ulcers in other neuropathic syndromes, e.g. myelodysplasia, old spinal cord injuries, syringomyelia, tabes, leprosy, and hereditary sensory syndrome.

Any persistent, nonhealing ulcer, particularly when it is associated with a callus, should alert the clinician to neurotrophism as a probable cause. Clinically, the diabetic ulcer is identical in all respects with its counterpart in tabes. With syphilis on the wane, and diabetes rapidly increasing, most such lesions are, today, diabetic in origin.

One is impressed with the loss of the normal architecture of the patient's feet. A broad splay metatarsus latus type of foot with hammer toes, hallux valgus, and prominent metatarsal heads is the rule. Characteristically, the ulcer has a punched-out appearance and is circular in shape (Fig. 1). There is often a vascular granular base, but it may be associated with infection and on occasion with a pregangrenous appearance. The size varies greatly from a pin-point opening to a huge area extending deeply to expose the underlying tendon (Fig. 2). However, the size of the ulcer is not necessarily related to the therapeutic response. The presence of strong pedal pulses and normal venous filling time and the resolution of the pregangrenous appearance with conservative management offer a sharp contrast to what is observed in patients affected with occlusive vascular disease.

Pathogenesis

Plantar ulcer is the result of the stress of walking on a foot with reduced nerve supply; it heals rapidly with any method that limits walking; and relapse takes



FIG. 1. Typical ulcer. Note circular, punched out appearance and surrounding callus.

place because walking is resumed after the cessation of treatment. Since the lesion is related to walking it occurs on the sole of the foot.

Neuropathy is an essential factor leading to the lesion and is characterized by the marked or complete loss of pain and temperature sensation; absent ankle jerks are the rule. The neurotrophic disturbance results in weakness and atrophy of the intrinsic muscles which produce characteristic deformities leading to the formation of chronic ulcers. The toes are held dorsiflexed at the metatarsal-phalangeal joints with flexion at the interphalangeal joints; this cocked-up position (claw toes) is that into which they are drawn by simultaneous contraction of the long flexors and extensors since the normal balancing force of the intrinsic muscles is removed (Fig. 3). As a consequence, the metatarsal heads are uncovered thus exposing them to more pressure and trauma. There is also thinning of the normal fat pads that overlay the metatarsal heads so that the latter can be palpated readily. The anterior arches soon become covered with a thick, hard callus. The crushing effect of body weight on the walking foot is added to a slipping that occurs between the bony framework of the foot and the ground beneath as each step is taken. The slipping is a response to the incompetent musculature. Added to this is the fact that, because of the abnormal alignment, the thrust of the body weight is borne by areas not originally designed by nature to absorb these blows. Thus the distribution of these ulcers is predictable at the site of maximum walking pressure, and reflects the mechanical factors.

In essence then, the ulcer is the result of gross pressure acting upon a devitalized area insensitive to pain. Ulcers on the surface of the metatarsal heads are always associated with thick, heavy callosities which precede their appearance.

It is significant to stress the vast difference in the problem posed by the neuropathic ulcer as distinguished from that resulting from vascular insufficiency for which the approach, treatment, and prognosis are entirely different.

"Atypical" location of ulcer. To support the interpretation of the pathogenesis as a stress placed on inappropriate receptive sites in the presence of impaired sensitivity are the following illustrative cases:

1) A diabetic was referred with a neuropathic ulcer over the fifth metatarsal head. The ulcer was atypical in that instead of being circular and punched out, it was irregular, angular, and pentagonal in shape (Fig. 4). Because of the bizarre configuration, further search was made. It developed that this man had been assiduous in his efforts to avoid athlete's foot and used a fungicidal powder in liberal quantity each morning. On examination of the shoe, there was found a

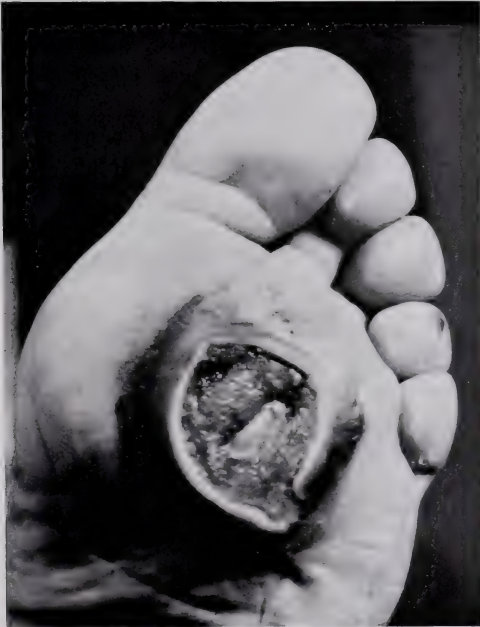


FIG. 2. Deep ulcer with exposed tendon.



Fig. 3. Interosseous muscle atrophy with characteristic deformity.

mound of coagulated powder corresponding to the ulcer in location and shape which had heaped up in a crack in the inner sole and impinged upon the foot causing the ulceration. By the simple expedient of removing the mound of powder, the ulcer healed rapidly and completely (Fig. 5).

2) Another patient, after a transmetatarsal operation, developed a large smooth circular ulceration at the midfoot—i.e., the site corresponding to the new weight-bearing area of the operated foot (Fig. 6). This again represents a neurotrophic ulcer occurring at the site of weight-bearing in an insensitive foot. This patient's ulcer was healed by diverting the pressure from this area with appropriate shoes.

3) We have had two cases of Charcot joints involving the metatarsal-tarsal bones with complete collapse of the arch of the foot. In each instance a classical neuropathic ulcer occurred far from the metatarsal heads but corresponding precisely to the new weight-bearing area wrought by the cataclysmic upheaval of the foot structure. One of these patients had an ulcer on the lateral margin of the foot corresponding to a displaced navicular bone occurring secondary to the shoe rubbing that area. On changing to a soft bedroom slipper, there was rapid and complete healing.

4) Further evidence of the presence of the effect of pressure and weight-bearing is the instance of a 54-year-old taxi cab driver in whom an ulcer developed



FIG. 4. "Atypical" ulcer.

at the base of the proximal phalanx of the right big toe. This unusual location was readily explained when he indicated that in driving, it was this area that he used for stepping on the accelerator pedal.

Therapy

The approach to therapy is conditioned by the fact that there are two aspects; 1) neuropathic and 2) mechanical. Since there is, at the present time, no specific therapy available for removing or reversing the neurological component, a method must be devised to eliminate or alleviate the responsible mechanical factors. Complete rest or a walking cast will relieve the mechanical factor, but unfortunately the lesion will recur on return to normal activity. Such recurrences may be eliminated by instituting debridement, trimming of the callus and antibiotics; these measures often produce healing. This must be followed by proper shoeing, diverting the weight-bearing from the affected areas to prevent further difficulties. Many ulcers are controlled by these means.



FIG. 5. Healed ulcer, depicted in Fig. 4.

In stubborn cases, excellent and lasting results may be obtained by excision of the metatarsal head in the base of the ulcer (5). In the presence of infection a two-stage procedure is advised; however, with modern day usage of antibiotics the infection can frequently be eliminated and the wound is usually closed by primary intention. Healing occurs since the blood supply is typically entirely adequate. This excision of the metatarsal head removes the immediate cause of the ulcer. Then, with proper shoes, including an inlay to distribute the weight more evenly, neurotrophic ulcers of this nature may remain healed indefinitely. Coventry (6), in a prolonged follow-up of five cases, four of whom were diabetic, reported excellent results with this procedure. This method is being increasingly used, and in our experience has been most satisfactory. Occasionally we have found it necessary to amputate the involved toe in addition to the metatarsal head.

Another approach to the surgical treatment has been proposed by McCook et al (1). Capitalizing on the knowledge that the tendons are flexed and the toes

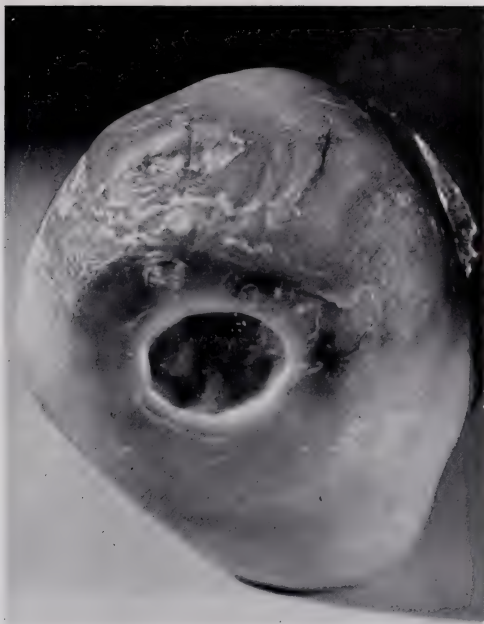


FIG. 6. Unusual ulcer location secondary to transmetatarsal operation.

are drawn up, they performed tenotomy of the flexors at the corresponding flexure of the metatarsal-phalangeal joint. They also utilized resection of the metatarsal head. Further experience is needed to evaluate the longtime effect of this technique.

Skin grafting has been recommended; our experience with this has been entirely unsatisfactory, as could be predicted.

Summary

Diabetic neurotrophic ulcer occurs in a foot with severe sensory impairment in the presence of good blood supply. Neurogenic small muscle atrophy results in abnormal foot alignment which forces the body weight to be borne by areas not originally designed for this purpose; the lesion is thus predictable at a site of pressure.

Treatment consists of the mechanical relief of pressure via proper shoeing aided by control of infection, debridement, and trimming of the callus. Should

simple measures fail, removal of the offending metatarsal head, followed by appropriate shoe appliances, is most effective.

In this series, other evidences of degenerative complications of diabetes were commonly present. At times, the ulcer was the initial clinical presenting manifestation, and a clue to the diagnosis of diabetes.

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Problems of Sterilization

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The specialty of obstetrics and gynecology is intimately concerned with human reproduction. We are interested in helping women to conceive and bear children when this is desired. We should be concerned just as much when it is desirable, or imperative, to prevent pregnancy and childbirth. Our subject, then, is conception control—and in this context, permanent, and, for the most part, irreversible birth control. This is in direct contrast to temporary contraception where the potential for future childbearing must be preserved.

In considering the problems of sterilization, let us discuss the medical aspects first. In our own field repeated caesarian section constitutes a justification for tubal ligation. In gynecology where extensive pelvic floor repair is being carried out, simultaneous sterilization should be done to prevent disruption of the reconstructive procedure.

In its broadest concept any medical condition in which future pregnancy would be contraindicated justifies sterilization. A few examples are serious renal or cardiovascular disease, neoplastic disease, advanced metabolic diseases such as diabetes, severe neurological, or mental illness. From the eugenic point of view where offspring are likely to inherit serious congenital defects—i.e.—Tay-Sachs disease, repeated mongolism, congenital neuroblastoma, as well as other abnormalities clearly related to chromosomal defects, surgical sterilization is essential. Mental retardation and insanity should also be considered in this group.

As for the socioeconomic considerations of this problem, many of us feel that a completed family, regardless of the number of children, is ample justification for voluntary sterilization. Even though it is legal in all fifty states we impose certain unrealistic restrictions for eligibility for sterilization on our patients. We insist that they have "X" number of babies by the time they are "Y" years of age to qualify. The magic formula seems to be "X times Y equals 120."

Unfortunately some hospitals confuse the issue and create a problem by having one committee to consider both therapeutic abortion and sterilization applications. We have just said that voluntary sterilization is legal in all fifty states. Why then should there be any committee to pass on sterilization? Only two states, Connecticut and Utah, have "restrictive legislation." They insist that a medical indication (not social or economic) be present. It should be noted, however, that under current acceptance of mental health, emotional stability, and peace of mind are elements of an individual's health. In this context, the World Health Organization has defined "Health" as being "not merely the absence of disease, but as a maximum state of physical, mental, and social well being."

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In this light, Connecticut and Utah should permit voluntary sterilization. A useful function of the combined committee is to offer sterilization with therapeutic abortion where the indication for the abortion is unlikely to change. However, simultaneous sterilization as a necessary condition for therapeutic abortion suggests a punitive measure, and this should be avoided.

Until very recently our "population explosion" presented a real threat to our civilization. The careful analysis of population trends may be summed up in Robert C. Cook's statement, "The most ominous force in the world today, next to the atom bomb, is uncontrolled human fertility" (1). Aldous Huxley has stated "A society that practices death control should practice birth control."

In his excellent review of voluntary sterilization, "Sex Without Babies," Dr. Curtis Wood (2) describes the population problem arising out of our unbalanced death-rate birth-rate ratio as bringing us to the "verge of a very destructive birth-quake."

The question of which partner should undergo sterilization is one that the physician can help decide in each individual case. When the wife is having a repeat caesarian section or gynecological surgery, tubal ligation would seem to be the method of choice. On the other hand, the simplicity and safety of vasectomy—a ten minute procedure under local anesthesia, often done in the doctor's office—has become more and more popular. The figures of our Association for Voluntary Sterilization here in New York show that half of all sterilizations in this country are now done in the male.

When sterilization is to be performed it is essential that the physician clarify all the aspects involved to both partners. These should include the nature of the procedure and the result, the finality and probable irreversibility of the operation, possible emotional reactions to it, and even the remote possibility of failure. I believe that it is of the utmost importance to project to the patient the possibility of a catastrophe to her children or her partner altering her wishes about future childbearing. I also stress the completely voluntary nature of the procedure.

Failure of tubal ligation and vasectomy have been reported as approximately one-half to one percent. Numerous studies have been published concerning medical, sexual, and psychosocial reactions to sterilization (3-5). They conclude that 95 to 98 percent of both male and female patients were completely satisfied with the operation. Our own Mount Sinai Hospital series has been reviewed and only two percent of the patients regretted having had the operation. On analysis, and this is in agreement with the literature, these were the few who had had incomplete understanding of what was being done, or underlying emotional problems that had not been resolved.

An occasion may arise in which reversal of a surgical sterilization becomes necessary. This can be done, and the rate of success in both female and male depends on the location of the section of the tube or vas. It is reported in the literature that the success rate ranges from twenty to sixty percent. In this connection, Dr. Albert Aldridge (6) of this city has reported on temporary surgical sterilization with reversal and subsequent pregnancy. His technique involves burying the fimbriated portion of the tube beneath the peritoneum of the broad

ligament. Even though undoing of the operation is possible, sterilization should be considered as a final, irreversible procedure.

The problem of voluntary sterilization cannot be discussed without considering the problem of abortion. Abortion, legal or illegal, is one of the chief methods of birth control in the world today. World population experts of the United Nations Conference in Belgrade in 1965 estimated that thirty million pregnancies are terminated intentionally each year. A survey of twenty-five years ago, before the so-called "Sexual Revolution," revealed that four out of five abortions in the United States were performed on married women. While these statistics are no longer valid, many married women with completed families turn to criminal abortion rather than have unplanned children. Certainly this group deserves permanent birth control, and sterilization in these women would save thousands of lives lost each year because of criminal abortion.

The Association for Voluntary Sterilization reports that approximately one hundred thousand Americans choose sterilization each year. Two factors should be stressed—people are marrying at an earlier age, and therefore completing their families at an earlier age. This means a long period of conception control. All the temporary methods of birth control leave much to be desired. Rhythm, condom, and diaphragm techniques fail all too often. In some patients oral contraceptives are inadvisable or specifically contraindicated. The intra-uterine device may be complicated by bleeding, expulsion, and perforation of the uterus. There is no question that there is a need for a method of birth control that is both permanent and safe, and surgical sterilization, whether performed on the male or female, fulfills these requirements. Forward-thinking people agree that couples have a right to increase their families, but that they also have a right to limit them permanently. Some physicians hesitate to perform sterilization because of the fear of legal reprisal under the ancient law concerning mayhem. Curtis Wood (7) has pointed out that there is no statute applicable to this because these operations are not mutilating procedures. The fact that vasectomy and tubal ligation are theoretically reversible excludes them from the category of mayhem which is defined as a permanent, mutilating injury.

The Association for Voluntary Sterilization has stated that no doctor has ever lost a suit if the operation was correctly done and proper consent had been obtained. A challenge to this statement was raised by the Knoxville, Tennessee "legend," according to which a husband successfully sued because his wife had been sterilized. The true facts of the case are most interesting. An unmarried woman on welfare decided that five illegitimate children were enough. The physician obtained proper consent in writing, performed the sterilization, and all went well until the patient married. The husband discovered that his wife had been sterilized, instituted a suit, and legend has it that the husband won the suit. Because of this story most of the physicians in Knoxville were reluctant to sterilize patients no matter how pressing the need. The truth of this matter is that the husband had sued his wife for divorce because she could have no children, and he won the suit. The law is clear in stating that a husband has no legal rights over the body of his wife prior to the marriage.

As previously stated, if the physician has taken the proper steps in explaining

the procedure fully, and has obtained a carefully-worded written consent from both the partners, he should have no fear of legal action. Our form is worded as follows: "We hereby request and consent to the procedure of sterilization by tubal ligation. The nature and probable consequences of this operation have been fully explained to us and, we understand that we may have no more children."

In all fairness to those who, for religious or moral reasons, do not agree with the principles of voluntary sterilization, no physician, nurse or hospital should ever be compelled to participate in the operation.

In conclusion, we have discussed some of the problems of sterilization. We have considered it from the medical, eugenic, socioeconomic, psychological, and legal points of view. As knowledgeable physicians in this field, we are in a position to offer an extremely important service to our patients and to the community.

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An Incision and Method of Wound Closure for Radical Mastectomy

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Mastectomy is a mutilating operation that causes disability and deformity. Although it is justified in the attempt to cure an otherwise fatal disease, any modification of the operation that can minimize the deformity without jeopardizing its effectiveness is desirable. Many skin incisions have been devised but none is completely satisfactory. The commonly employed vertical elliptical incision will often pass quite close to tumors located in the extreme upper outer quadrant of the breast, a common site of breast carcinoma. Closure often requires a skin graft. Oblique elliptical incisions extending over the shoulder toward the insertion of the pectoralis major muscle place the scar in a conspicuous site difficult to cover with ordinary clothing. Contraction of the scar may impair mobility of the shoulder. Transverse incisions are cosmetically more satisfactory but increase the difficulty of dissection of an axillary flap for exposure of the axilla. These incisions may pass quite close to tumors in the upper outer quadrant of the breast.

Any incision for mastectomy must satisfy several requirements. Primarily it must encompass the entire tumor with a sufficient margin of normal tissue to assure excision of all extensions. This aim cannot be accomplished if distant metastasis has occurred prior to the operation but the operation must be planned to assure the greatest probability of success when the disease is still localized. Many attempts have been made to assess the relative importance of various features of the operation by correlating them with the incidence of local recurrence. The incidence of local recurrences in wounds closed by skin grafts has been compared with the incidence in wounds without graft under the assumption that wider excision requires skin graft. All such studies have demonstrated either no difference or an increased incidence of local recurrence in the patients with skin grafts (1, 2, 3). This finding has then been explained away by the statement that the grafts must have been used for the patients with more extensive tumors. The original assumption may be one of the errors, for, within broad limits, the success of primary closure depends more on the shape of the defect and the technique of suture rather than on the size of the defect. More recent studies on the proximity of the tumor to the closest skin margin measured on the excised specimen have shown no correlation between the width of the margin and the incidences of skin recurrence beyond a margin of three centimeters (2, 3). For safety it would seem wise to plan any incision so as to provide a margin of five to six centimeters of normal tissue in all directions beyond the palpable edge of the tumor.

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In addition to adequate excision, the incision must provide access to the insertions of the pectoralis major and minor to facilitate their division to provide access to the axilla for dissection. Beyond this, closure should be possible without undue tension, although some tension on the skin flaps will decrease the tendency to accumulation of serum and lymph beneath the skin flaps. In the closed incision full thickness skin should cover the axillary vessels.

The scar should not cross the axilla in such a way as to interfere with motion of the arm. Transverse scars below the axilla will not affect mobility, although vertical incisions extending to the upper arm may interfere with function. Mobility of the shoulder is more dependent on scarring in the axilla from col-

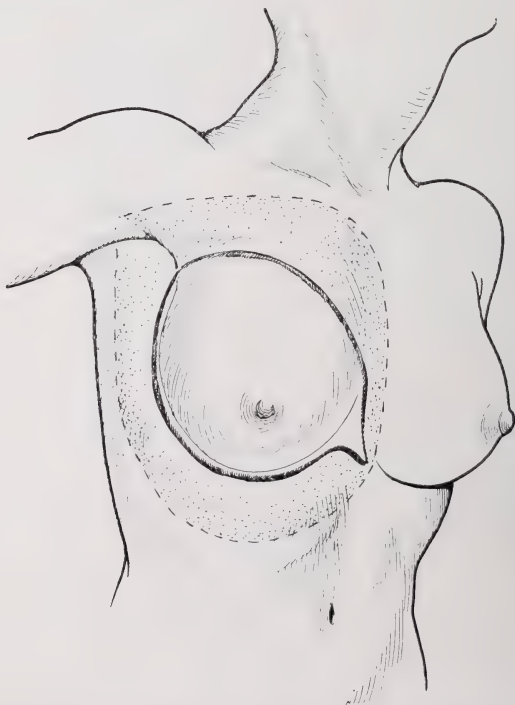


FIG. 1. Skin incision showing amount of skin removed and area to be undermined.

lections of blood or from infection. Serious interference with motion of the shoulder is almost always due to injury of the long thoracic nerve since the serratus anticus must fix the scapula before the arm can be abducted.

Consistent with the objectives of adequate skin incision and adequate exposure, deformity should be minimized. Thus an attempt should be made to place the scar in such a site that it can be readily covered and that patients can dress normally. Following mastectomy, patients are quite concerned about their appearance and their femininity. Emotional recovery is facilitated if they can dress normally and participate in all ordinary social activities. A scar that permits a low-cut dress, exposed shoulders, or bathing attire assists in their rehabilitation.

The incision described in this communication fulfills all the aforementioned requirements. It avoids linear extensions except as necessary to adjust skin flaps during closure. It provides access to the axilla. It can be closed in most instances without skin graft and when graft is necessary the graft does not approach the axillary vessels. The resultant scar is confined entirely to the chest wall and can be well covered by ordinary clothing. The incision is particularly suitable for tumors located in the upper outer quadrants of the breast.

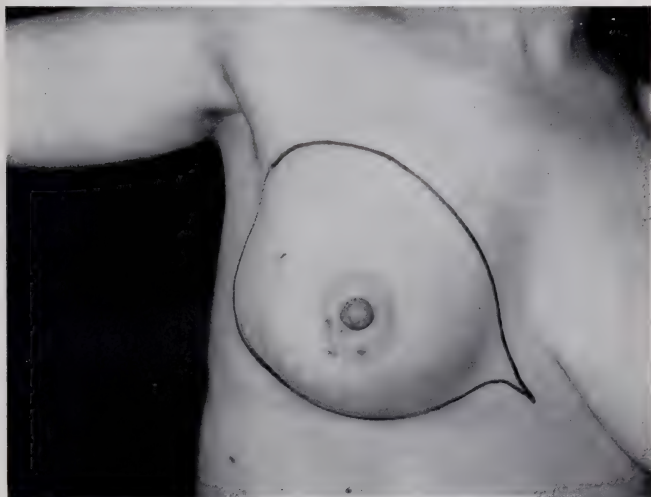


FIG. 2. Photograph of skin incision as outlined on a patient with a tumor in the upper outer quadrant of the breast.

Technique

The incision to be described was devised to adequately encompass tumors in the upper outer quadrant of the breast and in the axillary tail of the breast. Ease of closure after wide excision soon led to its use for most carcinomas of the breast except those located in the upper inner quadrant. The scar remains low. Most of it is hidden beneath a brassiere.

The technique of planning the incision is simple. Scratches are made on the skin six centimeters from the palpable edge of the tumor in all directions. They are extended to surround the remainder of the pedulous breast by a roughly pear-shaped oblique incision. Figure 1 shows the shape and extent of the skin incision and the additional area of skin to be undermined. Figures 2 and 3 show the incision as outlined on two patients, one with a normal-sized breast and one with a small breast.

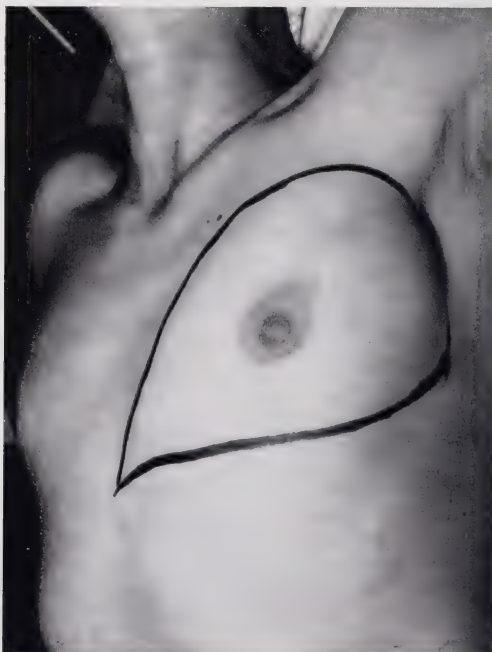


FIG. 3. Skin incision for mastectomy outlined for a patient with a small breast. This incision was closed without skin graft and healed completely.

Flaps are mobilized and the operation continued as described by Halsted and Haagenson (4). If necessary for adequate exposure of the axilla, vertical or transverse linear extensions can be made. These are seldom necessary. Adequate exposure of the insertion of the pectoralis major can be obtained by retracting the superior flap.

After the breast, pectoral muscles, the axillary contents are removed, a

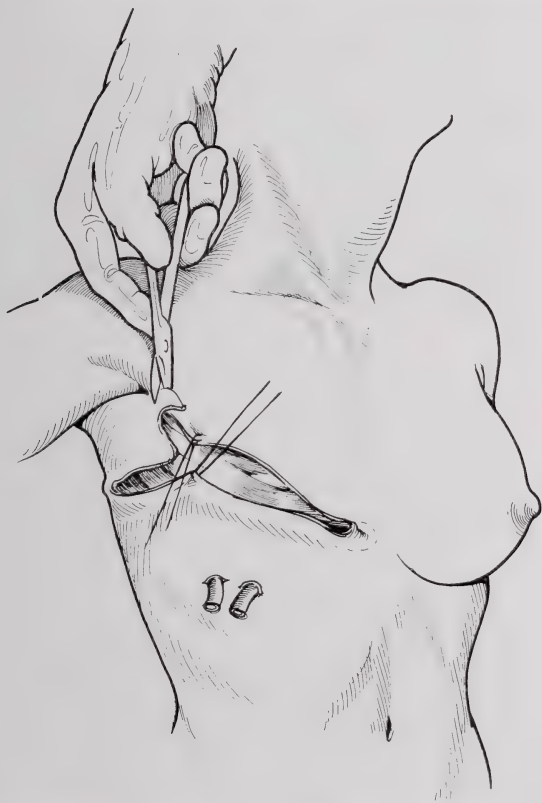


FIG. 4. Technique of closure. The lateral third of upper flap is brought medially and sutured to the central portion of the upper flap. Redundant skin at angles of the Y is excised.

large pear-shaped defect remains. The defect cannot be closed in either a vertical or transverse direction without undue tension. Because of the removal of the pectoralis major muscle and the consequent decrease in the circumference of the chest at that level there is some redundancy of skin of the upper flap in the axillary region. The lateral portion of the superior flap is brought medially and caudally converting the oval incision into a Y-shaped incision. The remaining defect is closed obliquely in a line extending from the region of the ensiform toward the axilla. Crescentic sections of skin at the ends of the short limbs of the Y are removed in order to eliminate prominence of these angles. Figure 4 shows the development of an axillary flap and the conversion of the oval into a Y. Figure 5 shows the sutured wound.

It is remarkable how large a defect can be closed in this fashion particularly if the sutures are taken close to the skin edge. Retention sutures are avoided

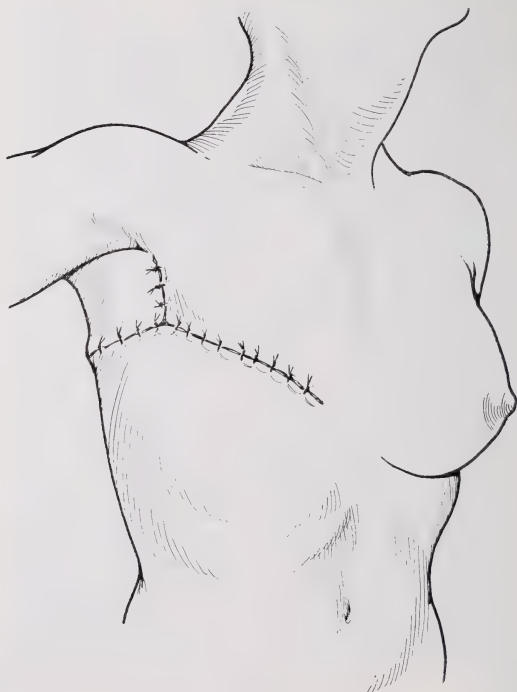


FIG. 5. Sutured incision.



FIG. 6. Incision one week after operation showing uncomplicated healing.

assiduously since they greatly increase the chance of necrosis of skin flaps. If the skin can be held with 0000 (4-0) silk sutures the tension is easily tolerated and skin necrosis will not occur. Figure 6 shows an incision one week after operation demonstrating the quality of healing to be anticipated. If the defect cannot be closed, an arrowhead-shaped graft is easily placed in the center of the closure well away from the axillary vessel (fig. 7). Frequently, an adequate amount of skin for the graft can be obtained from the crescentic excisions of redundant skin at the ends of the short arms of the Y closure. After removal of all subcutaneous fat they make excellent full thickness grafts.

Drains are placed for suction drainage whether or not a graft is used. This prompts rapid adherence of the skin flaps to the chest wall and decreases the incidence of postoperative serum formation. The drains are left for five to six days. Sutures are removed gradually and are not completely removed for fourteen days. Motion of the arms is generally quite free and the range of motion is complete within four to six weeks of the time of operation. Although this incision extends below the axilla, in no case has this caused any limitation of motion at the shoulder. Figures 8 and 9 show the appearance of the wound after healing is complete and illustrate the complete range of motion regularly achieved.

Discussion

Halsted (5) in his first description of the operation of radical mastectomy illustrated a circular incision around the breast with a curved extension over

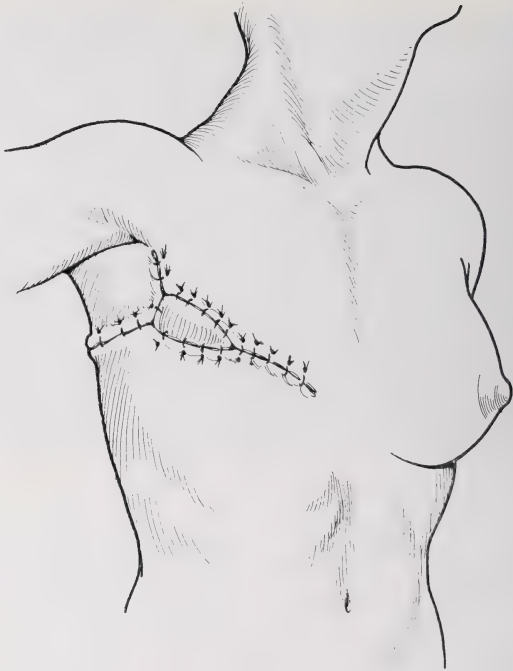


FIG. 7. Closure with small skin graft in area of greatest tension.

the shoulder and a vertical extension toward the clavicle. He subsequently modified the incision by eliminating the curved extension and substituting vertical extensions above and below the midline of the breast.

Still later he stated that he had gradually modified his incision making the vertical incision to the clavicle as short as possible and "when considerable skin has been removed above it may be altogether eliminated. Not infrequently, the only incision of the skin is the circular one surrounding the tumor" (6).

Meyer's incision, described at the same time as Halsted's first paper, was roughly obliquely elliptical with oblique curved linear extensions at the outer superior corner and at the inferior medial corner, the latter towards the ensiform, the former over the shoulder (8).

Halsted found it necessary to use split thickness skin grafts to close the



FIG. 8. Scar one year after operation with arm at side demonstrating inconspicuous nature of the scar.

incision in almost all instances. Surgeons trained in this tradition have taught that an adequate mastectomy requires closure by split thickness graft. Meyer closed the majority of his incisions without skin graft. Surgeons trained in this tradition accomplished closure of the wound without skin graft in the majority of instances. Most surgeons adopted Dr. Halsted's second incision or the elliptical incision of Dr. Meyer. Halsted's later modification was apparently either overlooked or discarded.

Numerous modifications of the skin incision for mastectomy have been devised in attempts to provide either better access to the axilla or to facilitate closure of the wound without skin graft and without undue deformity or disability. Many of these are quite complex and entail the fashioning of large pedunculated skin flaps. MacFee (7) tabulated twenty-eight modifications. He also described a subaxillary incision similar to one described by Orr (10) that had the advantage of placing the scar in the site that is less conspicuous than earlier incisions permitting women to dress more normally after the operation. Fourteen incisions are well illustrated in Madden's *Atlas of Techniques in Surgery* (8).

The incision described herein is a modification of the incisions of MacFee, Greenough, and Orr. It is similar to Halsted's final modification of his incision in that it avoids linear extensions except as necessary to adjust the skin



FIG. 9. Scar one year after operation with arm elevated demonstrating complete range of motion at the shoulder.

flaps during closure of the wound. This incision, as well as those of Orr, Greenough, and MacFee, is particularly suitable for tumors located in the upper outer quadrant of the breast, the commonest site of breast carcinoma. The more customary incisions may pass quite close to tumors in this location.

Summary

An incision for radical mastectomy that avoids a scar above the axilla is described.

It permits, in the majority of instances, closure without skin graft after excision of a wide margin of skin around the tumor.

It is particularly adaptable to tumors located in the upper outer quadrant of the breast.

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CLINICO-PATHOLOGICAL CONFERENCE

Sickle Cell Anemia Complicated by Anuria

Edited by

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A 43-year-old Negro male was transferred to The Mount Sinai Hospital because of anuria of ten days' duration.

At six years of age a splenectomy was performed for sickle cell anemia. During childhood he complained of intermittent severe pain over the lumbo-sacral area, and at 40 years of age an ulcer of the leg developed which healed after several months. No other members of his family had a history of anemia.

Ten months prior to admission he was treated at another hospital for aseptic meningitis and bronchopneumonia. His blood pressure was normal. Physical examination revealed enlarged cervical, axillary and inguinal adenopathy. The hemoglobin was 6 gm% and the BUN was 14 mg%. There was a slight proteinuria, and an occasional red blood cell per high power field. A bone marrow aspiration was unsuccessful. An x-ray revealed aseptic necrosis of the head of the right femur and cholelithiasis.

He received several blood transfusions and following discharge remained well. Five weeks prior to entry he experienced headaches, anorexia, weakness, and midabdominal pain. The pain was intermittent, crampy in nature, without radiation, unrelated to meals and relieved by lying supine. He denied a recent sore throat, dysuria, joint pain, or exposure to toxins. He was readmitted to the hospital two weeks later. The hemoglobin was 3.5 mg%, BUN 114 mg%, creatinine 21 mg%, uric acid 18.8 mg%, calcium 8.6 mg%, and phosphorus 8.1 mg%. The urine specific gravity ranged between 1.009-1.015. The urine contained moderate amounts of protein, red cells, and red cell casts. Initially, he voided one liter of urine per day. However, on the third hospital day he was unable to void spontaneously, and subsequently passed only 30-40 cc of smoky-appearing urine per day. A retrograde pyelogram revealed normal-sized kidneys and no obstruction. He received two units of packed red blood cells, and on the ninth day peritoneal dialysis was initiated. Dialysis was unsatisfactory because of technical difficulties related to the previous surgery, and he was transferred to The Mount Sinai Hospital for possible hemodialysis.

He was alert and afebrile but able to lie comfortably flat in bed. The blood pressure was 130/90, pulse 88 per minute, and respirations 20 per minute. The optic fundi showed arteriolar tortuosity. Râles were heard at the base of both lungs. The heart was normal. The liver was smooth, nontender and palpable three fingerbreadths below the right costal margin. He was not tender to percussion over the flanks. The cervical axillary and inguinal nodes were enlarged and were soft and rubbery. There was slight edema of the legs and sacrum.

From the Department of Pathology, the Mount Sinai Hospital, New York, N.Y.

The hemoglobin was 5.1 gm%, hematocrit 17.5, the white blood count was 6,800/mm³, with a shift to the left, and there were 28 normoblasts per 100 white blood cells. The platelet count was 115,000/mm³, and the reticulocyte count 2%. The red cells were hypochromic and target and burr forms were noted. The serum sodium was 137 mEq/L. The calcium was 7.6 mg% and phosphorus 8.7 mg%. Serial antistheptolysin titers were 833, 833, and 1250. A Coombs' test, serologic test for syphilis and LE preparation were negative. There was marked proteinuria and many red blood cells in the urinary sediment. A bone biopsy showed no marrow. An x-ray examination of the chest revealed prominent pulmonary vessels. An electrocardiogram showed left ventricular hypertrophy, a prolonged QT interval and peaked T waves in V₂-V₆.

Peritoneal dialysis was reinstituted with 15% solutions of Impersol. He received 30 exchanges each of approximately 2,000 cc. On the fourth hospital day dialysis was discontinued. The BUN was 57 mg%, creatinine 13.5 mg%, uric acid 8.0 mg%, calcium 10 mg%, phosphorus 5.0 mg%. The serum sodium was 142 mEq/L, potassium 4.6 mEq/L, chloride 96 mEq/L, and carbon dioxide 34 mEq/L. The serum albumin was 2.3 mg% and globulin 4.6 mg%. The serum alkaline phosphatase activity was 3.2 Bessie Lowry units. The SGOT was 18 units and prothrombin time 14 seconds. His weight remained unchanged. A retrograde inferior venogram showed patency of both renal veins. A renal biopsy was postponed because of a prolonged bleeding and clotting time. Anuria persisted, and he required eight units of packed cells to maintain the hematocrit above 20. By the tenth day his BUN had risen to 113 mg%, and he became lethargic and anorectic. Ampicillin and Keflin were given because of temperature elevations to 102°F. He complained of vague abdominal pain; however, the abdomen was soft and bowel sounds were normal. The chest x-ray was unchanged. Peritoneal dialysis was reinstituted four days later, and grossly bloody fluid was obtained which was attributed to insertion of the catheter. The fluid cleared and dialysis was continued. Colymycin was given intramuscularly for the persistent fever. Several blood cultures were sterile. Culture of the peritoneal fluid grew *B. pyocyaneus*.

The BUN decreased to 57 mg%, but by the 23rd hospital day rose to 114 mg%. The creatinine was 22 mg%. Dialysis was reinstituted. In addition, he received several units of whole blood for a persistent anemia. Forty-eight hours later his abdomen became distended and he complained of abdominal pain. Bowel sounds were diminished. A nasogastric tube was inserted following emesis of 1,000 cc of bile-stained fluid. An obstructive series showed multiple dilated loops of small intestine, and a dilatation of the transverse colon with loss of the normal haustral pattern. No obstruction or intrinsic lesions were demonstrated on the barium enema. There was narrowing of the sigmoid and descending colon, and absence of haustrations in the transverse colon. He received intravenous fluids. Gastric drainage and several stool examinations revealed occult blood. The BUN rose to 120 mg%, and he became confused and lethargic. After 48 hours of dialysis the BUN was 72 mg% and the serum electrolytes were normal. On the 34th hospital day he suffered aphasia and quadraparesis. A lumbar puncture was

traumatic, but the supernatant was clear. The platelet count was 12,000/mm³ and the hematocrit was 26. He expired 12 hours later.

*Dr. Marvin Goldstein**: This 43-year-old Negro man was transferred to The Mount Sinai Hospital because of anuria. A diagnosis of sickle cell anemia was apparently made in childhood, and at the age of six a splenectomy was performed. To most of us who normally see adults, splenomegaly in sickle cell anemia is unusual, but it must be remembered that in the first decade of life a considerable number of patients with sickle cell anemia have splenomegaly. That this patient had a splenectomy is also not surprising, since splenectomy was formerly the mode of treatment in children.

It is apparent from the history, that during childhood and early adult life, the manifestations of the sickle cell anemia were mild. During childhood he had only episodes of abdominal and epigastric pain. However, when he was 40 years of age a leg ulcer developed which healed very slowly, and 10 months prior to entry, he was hospitalized for an aseptic meningitis and bronchopneumonia. Both were probably manifestations of sickle cell disease.

A variety of neurologic abnormalities including drowsiness, stupor, coma, hemiparesis, aphasia, stiffness of the neck, blindness, and paresthesia also have been reported. Bacterial meningitis is often simulated by sickle cell anemia. Similarly, bronchopneumonia is frequently reported in sickle cell anemia, and is thought to be a consequence of the venostasis and small vessel thrombosis with resulting multiple small areas of infarction of the lung.

Three other manifestations of sickle cell anemia were noted on his hospitalization 10 months prior to his admission: aseptic necrosis of the head of the femur, cholelithiasis, and lymphadenopathy.

In view of the patient's subsequent illness, I think it is important to note that at this time the blood urea nitrogen and blood pressure were normal. The slight proteinuria and occasional red blood cells in the urinary sediment are not uncommon in patients with sickle cell anemia.

He remained well until five weeks prior to admission, when a combination of rather nonspecific symptoms developed: Headache, anorexia, weakness, and abdominal pain. On admission his anemia was much more severe than 10 months earlier, and there was evidence of marked renal insufficiency with a striking elevation of the blood urea nitrogen and the serum creatinine. The urine again showed proteinuria and red blood cells, but in addition there were red blood cell casts. Red blood cell casts, while not specific for any one renal disease, are strong evidence for the presence of a glomerulitis.

In the first two days of hospitalization he voided about a liter a day. While this volume would usually be considered normal, in the presence of the high BUN it suggests that there was a reduction in the number of functioning nephrons. From the third day of hospitalization to the time of his death, 34 days later, the patient was severely oliguric, excreting less than 40 cc a day, and this urine was described as "smoky appearing."

The physicians caring for the patient were concerned about the possibility of

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obstructive uropathy. A bilateral ureteral catheterization was performed, but no obstructing lesion was found and, more importantly, the kidneys were of normal size. It was decided, therefore, to perform peritoneal dialysis. Because of technical difficulties, the patient was transferred to The Mount Sinai Hospital.

On admission the blood pressure was 130/90 and he showed signs of a mildly congested state. The large, nontender liver probably was another manifestation of the sickle cell anemia. The peripheral blood smear was typical of hemolysis, and the serum electrolytes showed a moderate increase in potassium and decrease in CO_2 consistent with renal insufficiency. The ASLO titer was elevated and a definite rise in titer was noted, suggesting that the patient had a recent streptococcal infection.

The severe renal failure with anuria and a uremic syndrome required peritoneal dialysis on four occasions. During the second period of peritoneal dialysis, a culture of the peritoneal fluid grew a gram-negative organism. This finding does not necessarily indicate a peritonitis, since during peritoneal dialysis migration of bacteria from bowel into peritoneal fluid can occur.

In his last week of life, the patient experienced abdominal pain and distention. X-ray examinations of the abdomen showed a paralytic ileus, and a barium enema failed to demonstrate an intrinsic lesion of the colon. Occult blood was found in the gastric aspirate and stool. The abdominal findings may have been due to enterocolitis secondary to uremia, but they could also be a manifestation of the sickle cell anemia, that is, multiple small infarctions of the abdominal viscera and mesentery. Death occurred on the 34th hospital day when the patient became apathetic and quadraparetic.

In summary, this patient had a rather mild course of sickle cell disease until middle age, and then underwent profound renal failure. Death appeared to be secondary to a vascular accident within the central nervous system.

I would like Dr. Goldman to review the x-ray findings.

*Dr. Richard Goldman**: At the time of the patient's admission to this hospital, the x-ray of the chest showed a generalized enlargement of the heart. There was no evidence of specific single-chamber enlargement. The pulmonary vasculature was prominent and an interstitial process was seen throughout both lung fields. A scout film of the abdomen shortly before admission showed an enlarged liver and two or three calcified gallstones. The bones showed diffuse osteoporosis with a coarsening of the trabecular pattern. All of the vertebral bodies were compressed, and there were areas of infarction in the neck and heads of both femurs. An obstructive series during the last week in the hospital demonstrated dilatation of the small and large bowel consistent with an adynamic ileum. The barium enema, as Dr. Goldstein mentioned, did not show an intrinsic lesion of the colon. There was some free air in the peritoneal cavity secondary to peritoneal dialysis.

Bilateral venograms showed the renal veins on both sides to be patent. The renal contours, however, were not well visualized.

Dr. Goldstein: Dr. Goldman, did you see any evidence of calcification within the aorta?

* Resident, Department of Radiology, The Mount Sinai Hospital, New York, New York.

Dr. Goldman: No.

Dr. Goldstein: Thank you. In reviewing the protocol, I mentioned those physical and laboratory findings which are related to the sickle cell disease. The x-rays are also consistent with that diagnosis.

At this point, I would like to discuss the possible causes for the renal failure. Obstructive uropathy appears to have been ruled out. Possibly the renal failure was related to the sickle cell disease, since sickle cell disease does affect the kidneys. Albuminuria and microscopic hematuria are usually present. In addition, gross hematuria may occur in both sickle cell anemia and sickle trait. Gross hematuria, which characteristically appears in early adult life, occurs in males more than females, and is often painless and unilateral.

Another interesting aspect of the renal involvement in sickle cell disease is the inability of the adult patient to produce a maximally concentrated urine. This defect becomes progressively more severe with advancing years, and is not related to the severity of the anemia. A number of years ago we proposed that there is progressive damage to the medullary capillaries. These vessels then fail to act as counter-current exchanges, with the result that salt, which is normally transported into the medulla, cannot be retained at this site. The nephrotic syndrome has also been reported in sickle cell disease. However, whether the nephrotic syndrome is due to sickle cell disease or occurs by chance is unknown.

Finally, sickle cell disease produces changes in renal hemodynamics. The glomerular filtration rate, effective renal plasma flow and TMPah are all reduced by the third decade of life. However, this decrease in renal function is a gradual process occurring over a period of years and not, as in our patient, in less than a year. Thus death from renal failure in sickle cell disease rarely occurs.

The pathologic changes in the kidney in sickle cell disease appear to result from congestion and blockage of capillaries of the glomeruli, and the interstitial vessels by red blood cells. This leads to ischemia, necrosis and finally sclerosis of the glomeruli, and small areas of infarction in the renal parenchyma. Thrombosis of large vessels is not seen. In fact, thrombi in the kidney are extremely rare in any vessel greater than capillary size. In this case I expect the kidneys will show areas of microinfarction, glomeruli engorged with red cells, and even some sclerotic glomeruli. Since this patient's course does not appear to be the type of renal involvement usually described in sickle cell anemia, and since the blood urea nitrogen was normal 11 months prior to death, I do not believe sickle cell disease was responsible for renal failure.

Bilateral massive renal infarction due either to occlusion of the renal veins or renal arteries can cause acute renal failure. When renal vein thrombosis is rapid and bilateral, there is sudden oliguria, proteinuria, and rapidly advancing renal failure. If the inferior vena cava, as well as the renal veins is occluded, edema of the lower extremities is usually seen. The most common renal disease which gives rise to intrarenal venous thrombosis in adults is amyloidosis, and rarely chronic pyelonephritis. The angiogram, however, showed the renal veins were patent.

Bilateral renal artery occlusion can also produce renal failure. This disease is usually secondary to aortic atherosclerosis, occurs usually in elderly patients,

and if of sudden onset is usually accompanied by severe flank pains. I would exclude this diagnosis in this patient since he was only 43 years of age, and there was no evidence of aortic disease.

Other causes for acute renal failure and anuria include renal corticoncrosis, and diffuse vasculitis. From the information given in the protocol there is nothing to suggest these diagnoses. Also, I might add that acute tubular necrosis rarely causes prolonged anuria, that is, a urine output of less than 50 cc a day.

Finally, the end-stage of chronic renal failure appears unlikely in this patient because of the normal kidney size and the normal blood urea nitrogen 11 months prior to death. This leads me to a discussion of the disease I think produced the anuria, and rapid advancing renal failure. In the protocol we are told that on admission to the hospital the urine contained protein, red blood cells, and red blood cell casts. The casts, as I mentioned before, suggest the presence of a glomerulitis. In addition, on the third hospital day, when oliguria was noted, it was observed that the urine was smoky in appearance. Moreover, the physical examination suggested this patient was hypervolemic, manifested by pulmonary congestion and peripheral edema. Finally, we are told that the patient had an elevated ASLO titer. I think, therefore, the renal failure in this patient was produced by acute glomerular nephritis.

Acute glomerular nephritis produces a clinical picture of acute renal failure in less than five percent of cases, but most of these cases occur in adults. Characteristically, there is severe reduction in urine output. In fact, when obstructive uropathy has been ruled out as a cause of the anuria, acute glomerular nephritis probably is the most likely diagnosis. In recent years we have learned that acute glomerular nephritis is not a disease exclusively of childhood and early adult life. Many cases have not been reported in the fifth and sixth decades. However, the diagnosis of acute glomerular nephritis is often not considered in the adult because the clinical picture is frequently different.

In the adult, it is not uncommon for the patient to have rather nonspecific complaints, with no evidence of an antecedent infection. Hypertension and marked edema occur less frequently than in childhood. Significant hypertension and edema probably are not seen because the adult seeks medical attention early, before there has been retention of large amounts of salt and water in the body. The prognosis of acute glomerular nephritis in adults is relatively poor. In a review by Nesser and Robins in 1960, more than one-half of the patients dying of acute glomerular nephritis were more than 40 years of age.

As would be expected, the patients who die with anuria in the acute phase of glomerular nephritis have a particularly severe glomerulitis. Very often this glomerulitis, in addition to showing the usual cellular proliferation of the glomerular tuft, also shows a rather striking proliferation of the cells of Bowman's capsule. It is this capsulitis, along with the glomerular tuft hypercellularity, which apparently leads to the severe glomerular ischemia and the rapid development of obsolete glomeruli.

The patient died within 12 hours after the sudden onset of aphasia and quadraparesis, suggesting multiple discrete lesions involving the dominant cerebral

hemisphere and also the midbrain or the upper cord. Conceivably, a diffuse bilateral cerebral cortical lesion could be responsible. There are at least two causes for central nervous system vascular disease in this patient. In sickle cell anemia, thrombosis of cerebral capillaries and veins with multiple areas of infarction are not infrequently found. Thrombosis of the venous sinuses has also been reported. Bilateral signs and aphasia in this patient could be the result of multiple superficial cerebral vein thrombosis and finally thrombosis of the superior longitudinal sinus. A second possibility is that there was diffuse intracerebral bleeding secondary to thrombocytopenia. The thrombocytopenia could be due to the uremia, or to gram-negative sepsis. Since the spinal fluid was clear, thrombosis rather than hemorrhage is more probable.

My final diagnoses are: 1) Sickle cell anemia with lesions involving bone, lung, and central nervous system; 2) cholelithiasis, secondary to chronic hemolysis; 3) acute renal failure, secondary to acute glomerulonephritis.

The patient died from a cerebral vascular accident.

*Dr. Brian Vitsky**: Are there any questions for Dr. Goldstein?

Question: Acute renal cortical necrosis with disseminated intravascular coagulation could explain the patient's abdominal renal and central nervous system findings.

Dr. Goldstein: I excluded that diagnosis rather rapidly since I am unaware of renal cortical necrosis in sickle cell anemia. Therefore, I would have had to postulate an intraabdominal catastrophe with secondary renal cortical necrosis. However, the history and the physical findings can be amply explained by sickle cell anemia.

Question: Did he ever become hypertensive?

Dr. Vitsky: He did not.

Dr. Goldstein: In the adult it is not unusual for the blood pressure to be only modestly elevated. In addition, this patient had peritoneal dialysis at intervals throughout his hospitalization.

Dr. Vitsky: The brain and spinal cord were normal, and no anatomical explanation was found for his terminal neurological state.

The pleural cavities each contained approximately 50 cc of serous fluid and the peritoneal cavity contained 150 cc of cloudy pink fluid. There was a fibrinous exudate over most of the peritoneal surfaces, containing large numbers of polymorphonuclear leukocytes. *Aerobacter aerogenes* was cultured from the ascitic fluid at the time of autopsy. A post mortem blood culture was sterile. In addition, there was a small left, subphrenic abscess.

The pericardial sac contained only a few milliliters of serous fluid. There were no pericardial adhesions of exudate visible on gross examination. On microscopic examination, there was edema of the epicardium and an increased number of polymorphonuclear leukocytes and lymphocytes consistent with a mild uremic pericarditis.

The heart showed mild dilatation and hypertrophy of all chambers, and was slightly increased in weight. There was no evidence of valvular disease, and the

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main coronary arteries were widely patent. There was very mild subendocardial and perivascular fibrosis, but the small vessels appeared normal.

The lungs were congested and edematous. There was very mild dilatation and atherosclerosis of the main pulmonary arteries, and there was organized thrombosis of occasional small arteries. There was a diffuse interstitial fibrosis of varying severity, which is nonspecific and may be related to thrombosis and localized infarctions of the lung, or possibly to a healed interstitial inflammatory process. There were also a few "heart failure" cells containing hemosiderin pigment, and a very mild acute bronchitis.

The gastrointestinal tract was normal except for foci of necrosis of the gastric mucosa, as seen in uremia, or related to nasogastric intubation. This accounts for the occult blood in the stools and gastric aspirate.

The liver was moderately enlarged, congested, and edematous. It was markedly brown in color. The architecture was normal. Microscopically, there was very slight fibrous thickening of the central veins, and prominent iron pigment in the parenchymal and the Kupffer cells. There was central lobular congestion. The portal tracts were slightly fibrotic and there was extramedullary hematopoiesis in the portal tracts and throughout the sinusoids. Iron pigment was prominent in the parenchymal cells (Fig. 1.) The biliary tree was normal except for two large mixed stones in the gallbladder.

The pancreas was normal except for a single small focus observed of extramedullary hematopoiesis.

The vertebral bone marrow was compressed and flattened secondary to osteoporosis. The central areas of the vertebral bodies were soft and red. On micro-

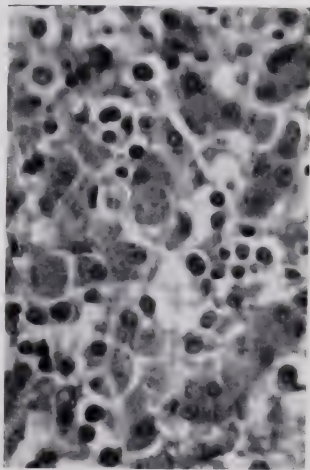


FIG. 1. Liver showing extramedullary hematopoiesis and hemosiderin deposition in Kupffer cells and parenchymal cells (hematoxylin and eosin $\times 400$).

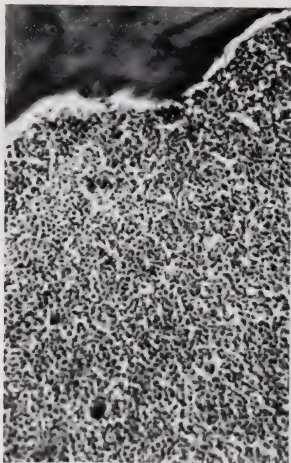


FIG. 2. Bone marrow demonstrating marked hyperplasia (hematoxylin and eosin $\times 100$).

scopic examination the marrow showed prominent erythroid activity (Fig. 2). The periphery of the vertebral bodies was firm and fibrotic (Fig. 3). The fibrotic changes were presumably due to old thrombosis and infarction.

The lymph nodes were enlarged throughout the body, but had normal architecture. There was prominent reticuloendothelial hyperplasia, dilatation of capillaries, and small foci of extramedullary hematopoiesis. Within the dilated capillaries were macrophages which contained phagocytized blood cells which is quite common in chronic hemolytic anemias (Fig. 4).

The kidneys were of normal size. The major arterial branches were widely patent and there was no evidence of urinary tract obstruction. The renal veins were widely patent. There were a few scars secondary to small vascular occlusions, and there were a few small petechiae on the external surface. The majority of the small arteries were patent, showing only slight intimal thickening. The glomeruli were normal in number, but they were all almost entirely hyalinized (Fig. 5). The capillary loops were not identifiable. Special stains showed only a few fragments of the basement membranes of the capillaries (Fig. 6). In approximately ten percent of the glomeruli there were remnants of crescents about Bowman's capsule. These changes were diagnostic of a diffuse glomerular nephritis. The tubules were slightly atrophic. In some dilated tubules within the medulla, there were pigmented and hyaline casts, commonly seen in renal failure with oliguria. The interstitial infiltrate of lymphocytes and plasma cells was also present. Other changes related to the sickle cell anemia were found. There was marked fibrosis of the medulla, a change which has been related to inability to concentrate urine.

FIG. 3. Fibrotic area in vertebral bone marrow (hematoxylin and eosin $\times 100$).

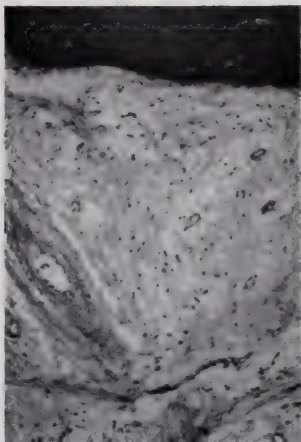
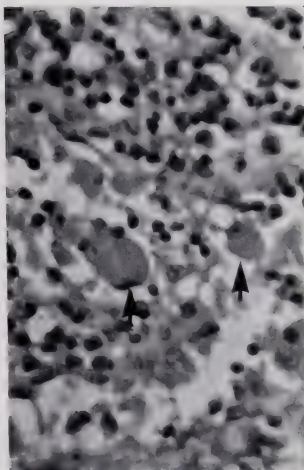


FIG. 4. Erythrophagocytosis (arrows) in a lymph node (hematoxylin and eosin $\times 400$).



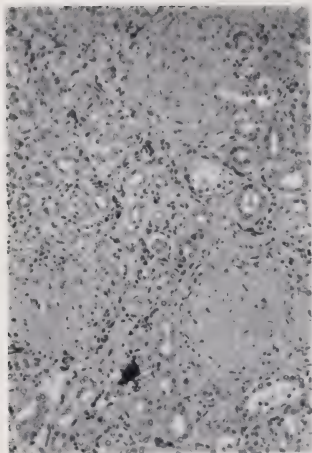


FIG. 5. Renal cortex showing hyalinized glomeruli (hematoxylin and eosin $\times 100$).

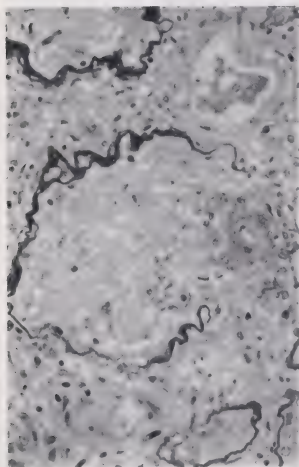


FIG. 6. A residual crescent and fragmented capillary basement membrane in a renal glomerulus (periodic acid Schiff $\times 250$).

This patient apparently had the rapidly progressive form of acute glomerular nephritis, characterized by extensive crescent formation, as well as proliferative changes in the glomeruli and obliteration of Bowman's space. Fibrinoid necrosis of the glomerular tufts is sometimes noted in these cases. With the increased use of peritoneal and hemodialysis, patients may survive long enough for these changes to progress to complete destruction and hyalinization may be seen within two weeks, and total hyalinization of the glomeruli in less than two months. In one biopsy study, hyalinization of glomeruli was evident within 15 days of the clinical onset of disease. In other words, changes formerly regarded as characteristic of chronic or subchronic glomerular nephritis may actually be found in what is clinically acute or subacute glomerulonephritis if the patient's survival time is increased.

In summary, the patient had a rapidly progressive glomerular nephritis, and the anatomical changes typical of sickle cell anemia.

Dr. Goldstein: I have to assume that the abscess and peritoneal changes could have been the consequence of the peritoneal dialysis. A renal biopsy in this case would have been a very useful means in deciding when to terminate treatment. In the last several years, we have had the opportunity of performing percutaneous renal biopsies after a reasonable period of peritoneal dialysis or hemodialysis. A biopsy that contains a representative number of glomeruli, for example, greater than 10, showing severe degeneration of the glomeruli, indicates that continual hemodialysis or peritoneal dialysis will not result in recovery of renal function, and that transplantation is the only alternative.

Finally, "subacute" glomerular nephritis is a pathologic diagnosis, since these patients by clinical standards have acute glomerular nephritis.

Question: Does the loss of concentrating ability suggest the patient had pre-existing renal disease?

Dr. Goldstein: At 43 years of age it would be exceptional if a patient with sickle cell anemia did not have loss of concentrating ability.

Final Diagnoses: 1. RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (SUBCHRONIC STAGE).

2. HYPERPLASIA OF BONE MARROW WITH FOCAL FIBROSIS.
3. EXTRAMEDULLARY HEMATOPOIESIS, LIVER, PANCREAS, LYMPH NODES.
4. HEMOSIDEROSIS, LIVER, RENAL TUBULES.
5. INTERSTITIAL FIBROSIS OF LUNGS, MODERATE.
6. MEDULLARY FIBROSIS OF KIDNEYS.
7. CHOLELITHIASIS.
8. SUBACUTE PERITONITIS AND LEFT SUBPHRENIC ABSCESS.

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RADIOLOGICAL NOTES

CLAUDE BLOCH, M.D. AND HARVEY M. PECK, M.D., Co-Editors

CASE NO. 312

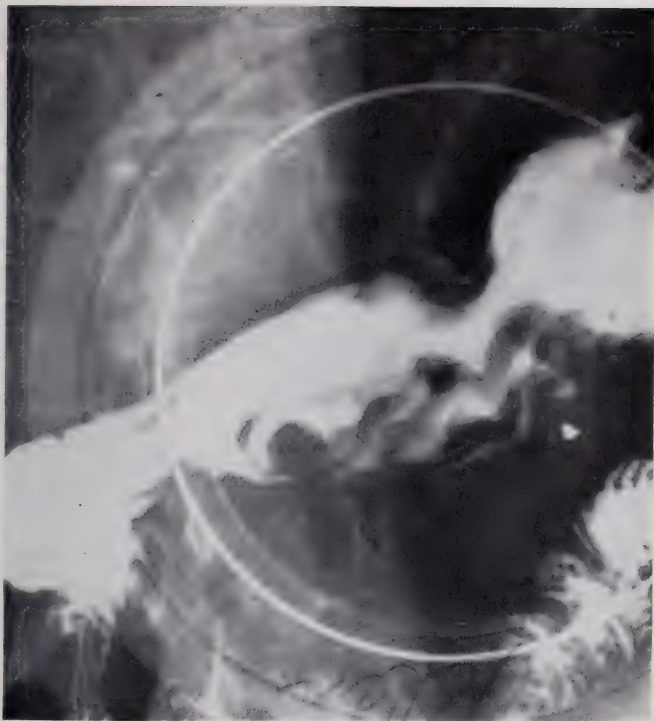
SUBMITTED BY RHONA J. KELLER, M.D.

A 60-year-old man was first seen at The Mount Sinai Hospital in 1963. He had a one-year history of severe episodic upper abdominal pain. Upper gastrointestinal series at that time revealed several sharply defined, smooth, rounded defects of various sizes within the lumen of the stomach. The lesions appeared continuous with the gastric rugal folds (Fig. 1). Discrete pedicles were not demonstrated. No contour defect was delineated at the site of the lesions. At surgery, a lesser curvature gastrotomy was performed and the biopsy from the area was interpreted as showing polypoid gastritis. The patient's symptoms recurred in 1964 and, because of continuing episodes of abdominal pain an upper gastrointestinal series was performed in 1966. This study revealed no appreciable change in the appearance of the gastric lesions. The multiple intraluminal defects were once more demonstrated (Fig. 2). The largest of these defects was clearly visualized along the greater curvature aspect of the gastric body. A contour defect in the area, however, was not seen and no ulceration was identified. Persistent abdominal pain required readmission to the hospital in 1968. Barium meal examination at this time revealed an increase in size and change in configuration of some of the intraluminal defects. The lesion along the greater curvature aspect of the body described above demonstrated considerable increase in size and definite lobulation of its contour (Fig. 3). Distortion of the gastric wall and a possible contour defect was suspected on some of the films at the site of this lesion. At gastroscopy numerous polypoid masses were noted in the antrum and distal one-half of the body of the stomach. The mucosa appeared congested and fresh bleeding was reported. A subtotal gastrectomy was performed. Examination of the surgical specimen revealed large rugae and multiple sessile polypoid formations (0.5 to 1.5 cm in diameter) clustered together (Fig. 4). These were soft and not adherent to the submucosal layers. A histological diagnosis of multiple adenomatous polyps was made. The patient suffered a stormy postoperative course with prolonged obstruction at the gastrojejunostomy anastomotic site. Patency of the stoma was finally achieved through conservative management including steroid administration and the patient was discharged from the hospital in satisfactory condition.

Discussion of Cases Nos. 312 and 313

The term gastric polyp refers to all benign epithelial tumors of the stomach. The general incidence at autopsy is less than one percent. Polyps are almost

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Case 312, Fig. 1. (1963) Several sharply defined, smooth, intraluminal defects of varying size are evident in the body of the stomach. The lesions appear continuous with prominent rugal folds. A large polyp is clearly seen along the greater curvature aspect of the stomach.

always found in the older age group. Hypochlorhydria or achlorhydria is the most common accompanying clinical feature although epigastric discomfort and upper gastrointestinal bleeding have been reported.

Gastric polyps are of two types. The first refers to the sessile or pedunculated adenomas occurring within an atrophic mucosa, often associated with atrophic gastritis, intrinsic factor deficiency, or symptomatic pernicious anemia. The second comprises the "well-demarcated elevations" associated with hy-



Case 312, Fig. 2. (1966) The rather prominent intraluminal defects within the body of the stomach are again seen. The largest of these is noted along the greater curvature (arrow). No appreciable change has occurred since 1963.

pertrophic gastritis which may be true adenomas or inflammatory pseudopolyps.

Roentgenographically, gastric polyps present as sharply defined, smooth lesions, usually round or ellipsoidal in shape, intraluminal, and generally continuous with rugal folds. Pedunculated tumors may obstruct orifices or produce intussusception. Ulceration is not detected but superficial erosions may be seen gastroscopically. Differential diagnosis includes benign submucosal tumor, aberrant pancreatic tissue, prominent gastric folds, ingested material, and blood clots.



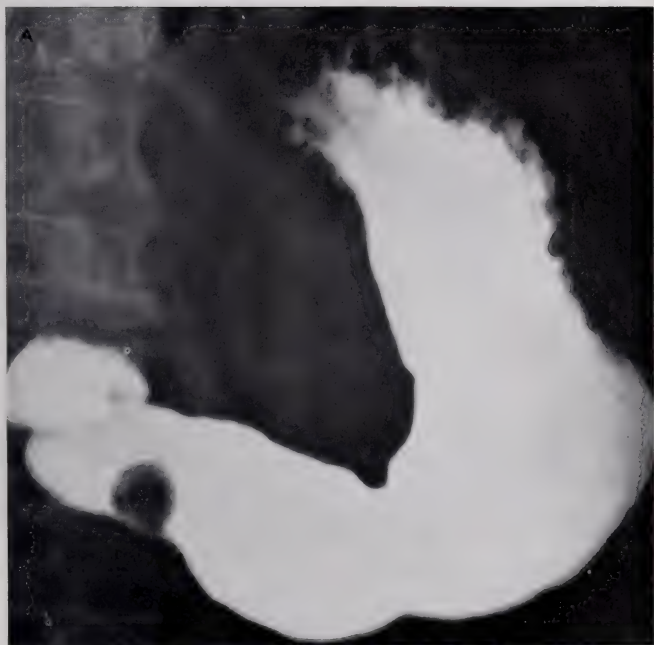
Case 312, Fig. 3. (1968) The number of intraluminal defects has increased. There now appears to be a large smooth but slightly irregular and lobulated defect along the greater curvature aspect of the body. There has been considerable change since 1966. At surgery, this defect was found to represent the confluence of several polypoid lesions.

The reported incidence of malignant degeneration of benign gastric polyps varies from 0% to 51% (1). Dr. Marshak and Dr. Feldman report a series of cases with roentgen findings as described above. No evidence of malignant transformation is noted over an average follow-up period of six years.

In addition to this case, a second case has recently been encountered demonstrating a gastric polyp in an elderly female with interval examinations over a period of five years (Case No. 313). Upper gastrointestinal examination in 1963 delineated a sharply defined, smooth, round, filling defect within the gastric antrum demonstrating no ulceration or contour defect (Fig. 1A). A well-developed pedicle was clearly demonstrated (Fig. 1B). A follow-up ex-



Case 312, Fig. 4. The photograph of the gross specimen showed the nodular masses along the rugal folds. No ulcerations are seen.



Case 313, Fig. 1A. There is a sharply demarcated intraluminal defect along the greater curvature of the gastric antrum. A small narrow pedicle is apparent. The remainder of the antrum is normal.



Case 313, Fig. 1B. During the course of the same examination, the polyp enters the duodenum and its stalk is now seen to be long and narrow.

amination of the stomach in 1968 revealed the polyp to have remained unchanged in size, shape, and configuration.

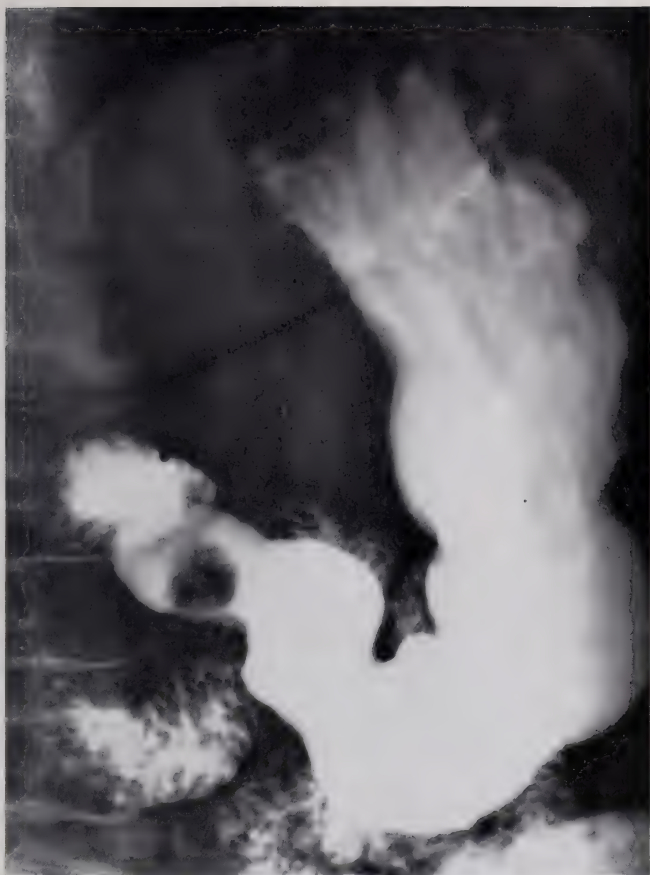
Case Report: GASTRIC POLYPS-LONG TERM FOLLOW-UP—REPORT OF TWO CASES

Acknowledgment

The editors wish to thank Drs. Henri Coleher and Leon Ginzberg for permission to publish Case No. 312 and Dr. Samuel K. Elster for Case No. 313.

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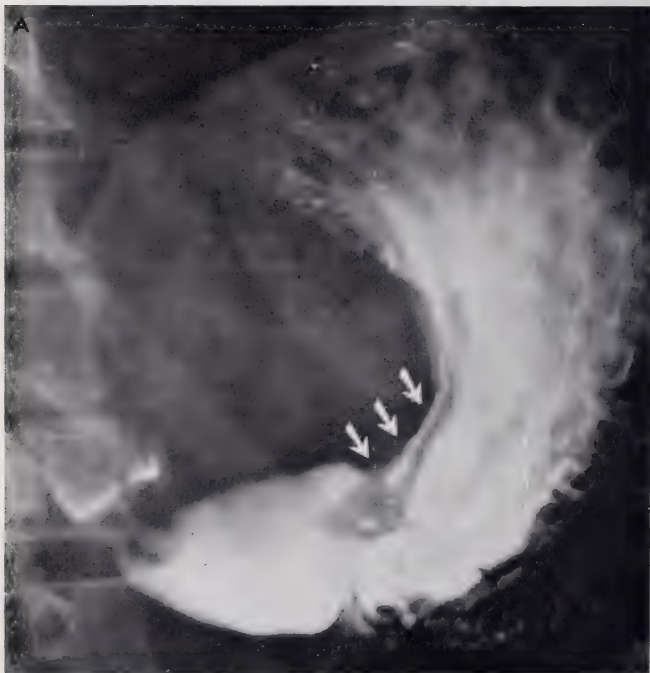
1. Marshak, R. H. and Feldman, F.: Gastric Polyp. *Am J Dig Dis* 10: 909-935, 1965.



Case 313, Fig. 2. Five years later, this patient who has continued to remain asymptomatic is noted to have the same lesion in the gastric antrum. It has remained unchanged in shape, size, and configuration.

CASE NO. 314

A 50-year-old man complained of vague epigastric pains, not related to meals and not relieved by food or antacids. There had been no anorexia or weight loss. An upper gastrointestinal series was performed which showed a constant area of decreased distensibility along a short segment of the lesser curvature, near the reentrant angle (Fig. 1). Although the rugal folds were slightly distorted and prominent in this region, no ulcerations or nodularity could be demonstrated. The patient was treated with a bland diet and anti-spasmodics. He was instructed to return for a follow-up in six weeks. He did



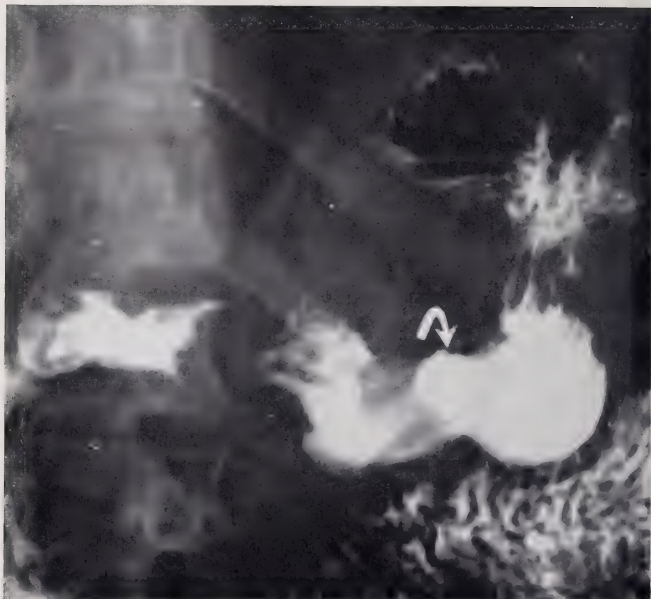
Case 314, Fig. 1A and 1B. Right anterior views of the stomach in various phases of filling, reveal an area of decreased distensibility within the lesser curvature near the reentrant angle (along arrows). The rugal folds are slightly more prominent than usual, but no ulcerations or nodularity of the wall are noted.



Fig. 1B.

(See legend under Fig. 1A)

not return for three years, at which time a repeat gastrointestinal series was performed. A large ulcer was then seen in the same portion of the lesser curvature. The ulcer did not extend as a niche beyond the confines of the stomach (Fig. 2). A symmetrical mound could be outlined when only a small amount of barium collected in this area. Distensibility of the lesser curvature could not be properly evaluated on this study, since no fluoroscopic information is available and none of the films showed a well-filled stomach either in the upright or horizontal position. The lesion was thought to represent a benign ulcer and again the patient was placed on a strict ulcer regimen. The patient failed to return after six weeks as instructed and instead a third gastrointestinal series was performed six months later. The stomach now revealed a rigid segment of the lesser curvature near the reentrant angle (Fig. 3A). The

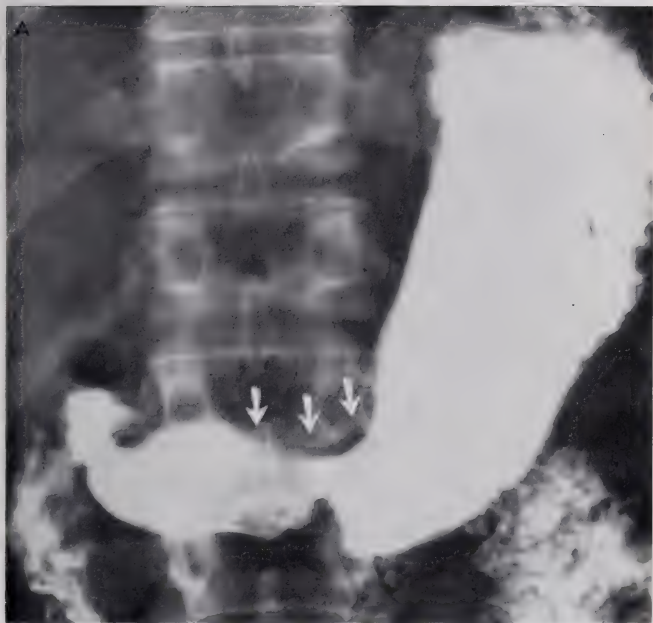


Case 314, Fig. 2. Repeat examination three years later, now reveals a large ulceration at the reentrant angle, presenting as a crater within the confines of the stomach. A symmetrical mound is noted around the ulcer when the stomach is partially empty.

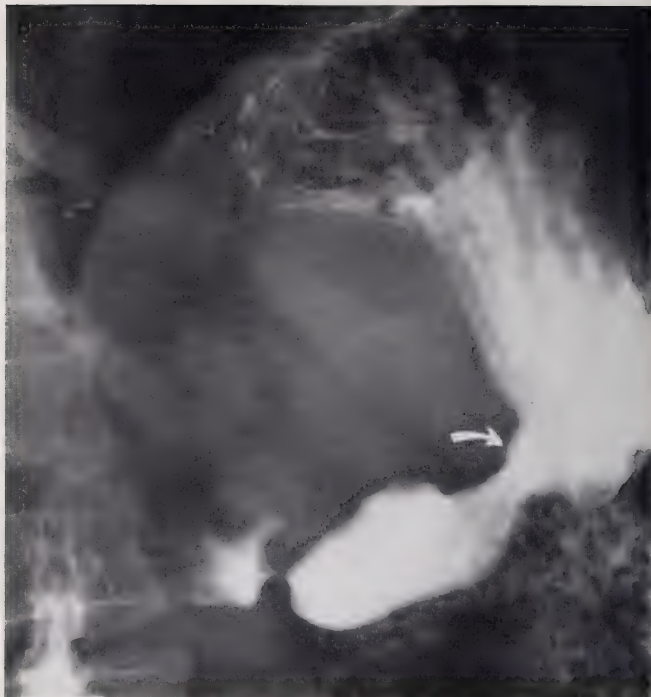
rugular folds were indistinct; no masses or nodularity of the contours of the the stomach could be demonstrated. When the stomach emptied partially, a smooth shallow ulceration could be seen within the affected segment (Fig. 3B). The patient was operated upon, and an extensive infiltrating carcinoma of the stomach was found, affecting much of the lesser curvature of the body. A high subtotal resection and gastroenterostomy were performed and the patient made an uneventful recovery.

Discussion

This is an unusually long and instructive follow-up of a gastric carcinoma. Of course it is a retrospective type of study, as the original two sets of x-rays were interpreted as representing direct or indirect evidence of a benign ulcer. It has been pointed out many times in the literature that any atypical



Case 314, Fig. 3A. Repeat examination six months later, ($3\frac{1}{2}$ years after Fig. 1), reveals marked decreased distensibility of the distal portion of the body of the stomach at the reentrant angle (along arrows). The rugal folds in this region are effaced.



Case 314, Fig. 3B. When only a small amount of barium is present within the stomach, a shallow smooth ulceration can be demonstrated (arrow) within the area of rigidity described in Fig. 3A.

features of an ulcer, or persistence of even a short segment of lessened distensibility after the niche has disappeared, must be regarded as highly suspicious of a malignant process. The concept of a "superficial spreading carcinoma" with a "benign" peptic ulcer within its wall is being accepted more and more by radiologists and pathologists. In these cases, no masses exist and the ulcer crater often looks entirely like a benign niche and can be seen to disappear under medical therapy. In these patients, the wall abnormalities, which are often subtle, are of prime importance in the differential diagnosis.

Case Report: GASTRIC CARCINOMA—THREE AND ONE-HALF YEAR FOLLOW-UP.

CASE NO. 315

A 70-year-old woman complained of abdominal pain and weight loss together with severe anorexia. An epigastric mass was palpated and a microcytic anemia was present. Barium enema examination was performed in order to



Case 315, Fig. 1A. The barium-filled colon in the anterioposterior view reveals a flattening of the superior portion of the transverse colon, just to the left of the midline (along arrows). Instead of the normal haustration, there is spiculation of the folds over a small segment of the colon. The inferior portion of the transverse colon, as well as the remainder of the large intestine appears normal.



Case 315, Fig. 1B. In the double contrast study, there is a suggestion of nodularity along the same short segment of the transverse colon (along arrows). The remainder of the colon again appears normal.

rule out a colonic neoplasm. Within the midportion of the transverse colon, just to the left of the midline, was a short flat contour defect affecting only the superior wall of the colon. The normal haustrations were replaced by irregular shallow spiculations (Fig. 1A). No masses could be outlined adjacent to the transverse colon. On the air contrast study (Fig. 1B) there was a suggestion of nodularity along the same contour of the transverse colon. The mucosa



Case 315, Fig. 1C. On the mucosal study, the folds appear intact, without ulcerations or other abnormalities.

over the affected segment appeared intact (Fig. 1C). Because the appearance suggested a serosal process—invasion over a short segment of colon—it was suggested that a gastric malignancy was probably responsible for the colonic findings. Thus an upper gastrointestinal series was performed, which revealed an extensive scirrhus carcinoma of the distal two-thirds of the stomach (Fig. 2). An exploratory laparotomy was performed and the gastric neoplasm was found to invade the transverse colon via the transverse mesocolon. It was deemed inoperable and only a biopsy was performed.

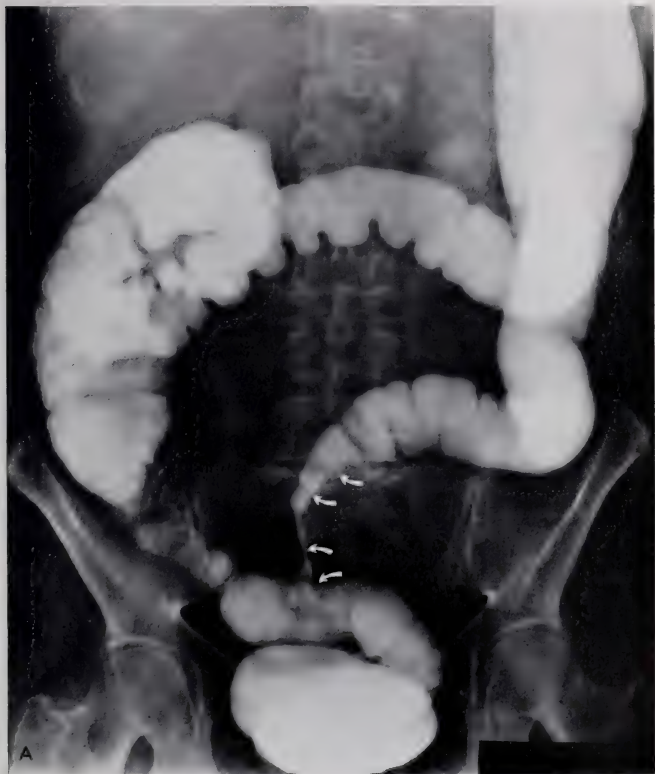
Case Report. METASTATIC LESION OF THE COLON—PRIMARY IN THE STOMACH.



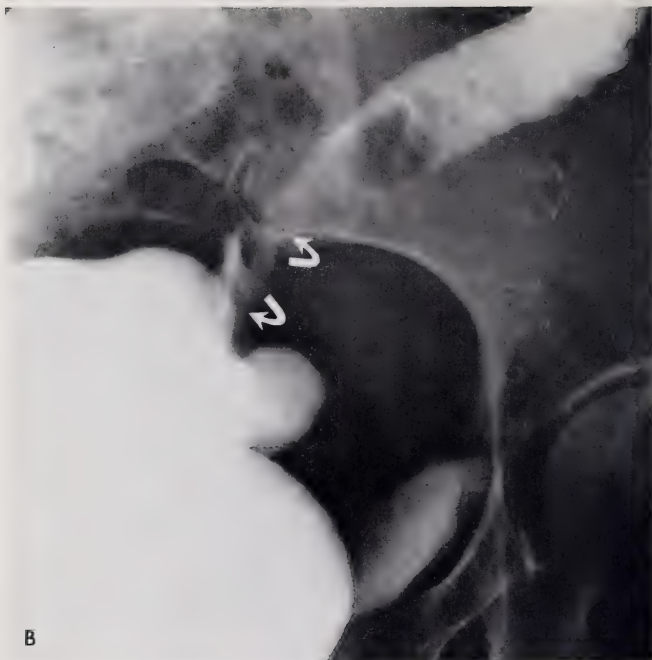
Case 315, Fig. 2. The extensive infiltrative carcinoma of the distal two-thirds of the stomach is noted with a shallow ulceration within the antrum (arrow).

Discussion of Cases Nos. 315, 316 and 317

Metastatic disease to the colon must be considered in any segmental lesion of the large intestine. These must be divided into two main types: Those with primary mural involvement, and those that represent extensions from



Case 316, Fig. 1A. There is a scalloped defect on the left lateral wall of the proximal sigmoid colon causing a double contour defect (along arrows). There is no proximal dilatation, ulceration, or overhanging edges. No soft tissue mass can be delineated in the left lower quadrant.



Case 316, Fig. 1B. These findings are again well demonstrated on a spot film of the sigmoid colon (along arrows).

an extracolonic mass. Characteristically, the mural lesions appear as broad-based flat nodular contour defects, usually with intact mucosa. These may present as single lesions, but more commonly multiple, as in serosal implants. When the colon is invaded from an adjacent mass, it first becomes displaced, then fixed (Case Nos. 315 and 317), and then narrowed (Case No. 317) by the growing malignancy. The most common primary sites are the stomach, pancreas, ovary, breast, lung, and kidney (1). Case No. 315 demonstrates a scirrhous carcinoma of the stomach invading a localized segment of the transverse colon via the transverse mesocolon. No adjoining masses, displacement or angulation could be demonstrated. Case No. 316 demonstrates invasion of the sigmoid by a retroperitoneal lipofibromyxosarcoma. A large mass could be demonstrated in the left lower quadrant which also caused partial obstruc-



Case 316, Fig. 2. A trapping film during intravenous pyelography reveals a moderate hydronephrosis on the left side down to the pelvic brim.

tion to the left ureter. The lesion of the descending colon in Case No. 317 turned out to be a serosal implant from a primary carcinoma of the ovary.

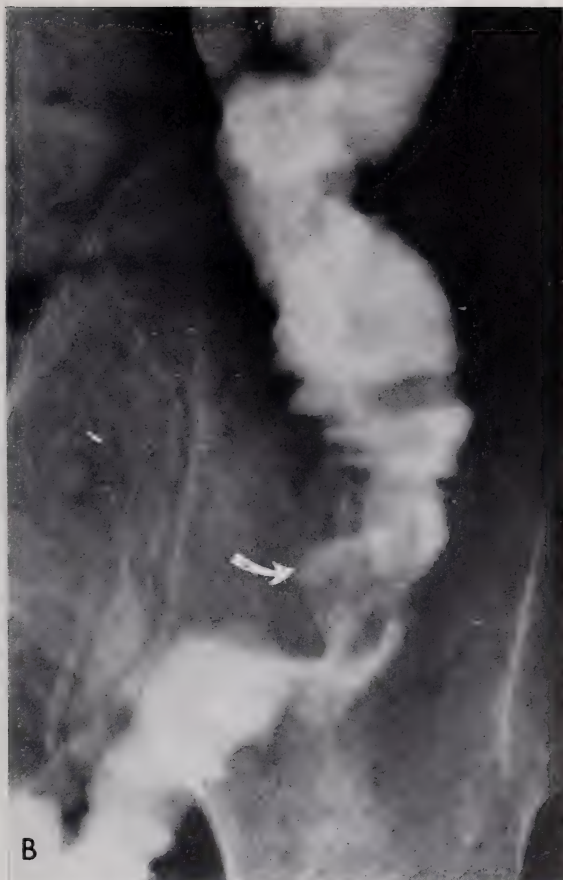
Case Reports: METASTATIC LESIONS TO THE COLON—REPORT OF THREE CASES.

Acknowledgment

The Editors wish to thank Drs. A. Daniel Hauser and Samuel Klein for permission to publish Case No. 315 and Dr. Samuel K. Elster for Case No. 316.



Case 317, Fig. 1A. The barium-filled colon in the left anterior oblique view reveals a scalloped lobulated contour defect along one wall of the mid-descending colon. There is no proximal dilatation; the opposite wall of the affected segment appears normally distensible.



Case 317, Fig. 1B. On a spot film of the same region, a small triangular amorphous collection of barium is noted (arrow), which probably represents a shallow ulceration.

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Received for publication September 3, 1968



INDEX TO VOLUME THIRTY-FIVE

- A**-beta-lipoproteinemia. (R. M. Sturman), 489
- Absorption. (A. M. Gelb), 429
- Acanthocytosis. (R. M. Sturman), 489
- Acrylamide gel electrophoresis, applications. (A. H. Wolintz, et al.), 174
- Afebrile bacterial endocarditis. (E. Teich), 566
- Allen, D., et al. Exercise in normal dogs under chloralose and urethane anesthesia, 265
- Alpert, L. I. Thrombotic thrombocytopenic purpura and systemic lupus erythematosus: Report of a case with immunofluorescent investigation of vascular lesions, 165
- An incision and method of wound closure for radical mastectomy. (G. Lesnick), 599
- Andelman, S. Radiological notes, 443, 444
- Androsterone, buccal, therapy of hirsutism: A preliminary report. (S. I. Griboff et al), 179
- Anemia
 due to penicillin. (L. J. Lyon), 258
 sickle cell. (CPC)
 small bowel postoperative blind loop. (Rad. Notes), 321
- Anesthesia
 in dogs, 265
- Aneurysm
 of splenic artery. (Rad. Notes), 447
- Anxiety
 in cancer patients (R. Blacher, et al), 423
 Psychotherapeutic drugs (J. Polenz, et al), 246
- Arthritis and rheumatism. (S. Davison, et al) 473
- Asch, S. S. Crib deaths: Their possible relationship to post-partum depression and infanticide, 214
- B**ACTERIAL endocarditis. (E. Teich), 566
- Bassen-Kornzweig syndrome. (R. M. Sturman), 489
- Beck, A. R., editor. See unusual problems in surgery
- Bilateral complete internal carotid artery occlusions in a patient with transient neurologic deficits. (L. D. Jacobs), 518
- Blacher, R. S. et al. The initial contact with the cancer patient—Some psychiatric considerations, 423
- Bloch, C., editor. See radiological notes.
- Bone
 Tumors of periosteal origin. (R. Zaretsky), 274
- Bowel, small
 Congenital abnormalities of the small bowel (Moseley and Rabinowitz), 14
 postoperative blind loop causing anemia, (Rad. Notes), 321
 recurrent myosarcoma in, (Rad. Notes), 102
- Breast cancer. (D. Sirota, et al), 242
 mastectomy. (G. Lesnick), 599
- Buccal androsterone therapy of hirsutism: A preliminary report. (S. I. Griboff, et al), 179
- Burrows, L., editor. See unusual problems in surgery
- C**ARCINOMA.
 breast. (D. Sirota, et al.), 242
 gastric, (Rad. Notes), 630
 in sigmoid blind loop (Rad. Notes), 318
 patient, psychiatric considerations (R. S. Blacher, et al), 423
 Thio-TEPA and methotrexate chemotherapy in advanced ovarian carcinoma (Greenspan), 52
- Cardiac valve replacement. (CPC), 526
- Carotid
 artery ligation, history of. (S. Gross), 221
 occlusive disease, bilateral. (L. D. Jacobs), 518
- Celiac syndrome. (R. M. Sturman), 489
- Cerebrovascular disease. (L. D. Jacobs), 518
- Chapman, I. Relationships of recent coronary artery occlusion and acute myocardial infarction, 149
- Chemotherapy
 Thio-TEPA and methotrexate-of advanced ovarian carcinoma (Greenspan), 52
- Cherubism. (Rad. Notes), 436
- Children-prognosis of granulomatous colitis in. (Korelitz), 1
 tuberculosis (J. G. Rabinowitz, et al), 479
- Chloralose. (P. D. Stein, et al.), 265
- Cholecystitis. (M. A. Naqvi, et al), 396
- Clinico-Pathological Conference, F. M. Klion, Editor
 fever, hepatosplenomegaly and pulmonary densities, 184
 hemoptysis, 307
 jaundice and congestive failure after cardiac valve replacement, 526
 pancytopenia and chronic pulmonary disease in an elderly male, 86
 sickle cell anemia complicated by anuria, 610
- Colitis, granulomatous-prognosis of with onset in childhood, (Korelitz), 1
- Colon, metastatic lesion of, (Rad. Notes), 635 and 639
- Colonic bezoar due to serutan. (Rad. Notes), 323
- Colp, Ralph Award, 107
- Concepts and treatment in polymyalgia rheumatica. (S. Davison, et al), 473
- Congenital abnormalities of the small bowel. (Moseley and Rabinowitz), 14
- Contralateral trigeminal neuralgia in meningiomas of the cerebellopontine angle. (P. Levin et al), 343

- Coombs' positive hemolytic anemia due to penicillin. (L. J. Lyon), 258
- Coronary artery disease: rest, repair, or replacement. (D. Harken), 541
- occlusion and acute myocardial infarction, relationships of. (I. Chapman), 149
- Creatine phosphokinase isoenzymes. (A. H. Wolintz et al.), 174
- Crib deaths: Their possible relationship to post-partum depression and infanticide. (S. S. Asch), 214
- Current trends in curriculum redesign. (H. Popper), 332
- Curriculum redesign. (H. Popper), 332
- D**ANESE, C. A. et al. Intraperitoneal hemorrhage as a complication of acute ruptured cholecystitis, 396
- Davison, S. et al. Concepts and treatment in polymyalgia rheumatica, 473
- Depression post-partum. (S. Asch), 214
- psychotherapeutic drugs. (J. Polenz et al), 246
- Development and goals of a trauma and shock research center. (W. Shoemaker, et al), 451
- Diabetes gangrene, surgery. (A. Singer), 390
- melittus. (CPC'), 307
- neuropathic ulcer. (M. Ellenberg), 585
- neuropathy of upper extremities. (M. Ellenberg), 134
- Discogenic spine pain and associated radiculitis in the N.Y.C. Fire Department. (A. J. Schein), 371
- Dreiling, D. A. et al. Intraperitoneal hemorrhage as a complication of acute ruptured cholecystitis, 396
- E**ARLY results with 20-femoro-popliteal vein bypass grafts for severe peripheral ischemia. (A. Singer and G. Rossi), 234
- Effect of varying fat diets on the incorporation of fatty acids into esters by the small intestine in vitro. (A. M. Gelb), 429
- Electrophoresis-Acrylamide gel. (A. H. Wolintz, et al.), 174
- Ellenberg, M. Diabetic neuropathy of the upper extremities, 134
- Diabetic neuropathic ulcer, 585
- Elwyn, D. H. et al. Development and goals of a trauma and shock research center, 451
- Endocarditis. (E. Teich), 566
- Eng, Y. F., et al. Metastatic infiltration of the thyroid gland causing hypothyroidism, 242
- Engel, W. K., et al. Isoenzymes of creatine phosphokinase determined by acrylamide gel electrophoresis, 174
- Eosinophilic meningitis, (S. Gendelman), 578
- Evolution and pathogenesis of discogenic spine pain and associated radiculitis as seen in the New York City Fire Department. (A. J. Schein), 371
- Exercise in normal dogs under chloralose and urethane anesthesia. (P. D. Stein, et al.), 265
- F**AT diet. (A. M. Gelb), 429
- Feder, S. L., et al. Psychotherapeutic drugs—patterns of use, 246
- Femoral popliteal vein bypass grafts. (Singer, A. et al), 234
- Fever, (E. Teich), 566
- Friedreich's ataxia. (R. M. Sturman), 489
- Futterweit, W., et al. Buccal androsterone therapy of hirsutism: A preliminary report, 179
- G**ABOR, G., et al. Exercise in normal dogs under chloralose and urethane anesthesia, 265
- Gastric carcinoma. (Rad. Notes), 630
- polyps. (Rad. Notes), 622
- Gelb, A. M. The effect of varying fat diets on the incorporation of fatty acids into esters by the small intestine in vitro, 429
- Gendelman, Seymour. Eosinophilic meningitis, 578
- Glass, J. R., et al. Therapy with radioisotopes: a general survey (excluding iodine), 68
- Gadbois, H. L., et al. High flow whole body hemodilution perfusion: Acid base, renal electrolyte and body fluid alterations, 111
- Obituary, 329
- Gangrene, in diabetes. (A. Singer et al), 390
- Geriatrics—institutional care facilities in N.Y.C. (M. Rogin et al), 358
- Goldfarb, A. et al. Institutional care facilities for older people in New York City, 358
- Goldfield, E. B., et al. Metastatic infiltration of the thyroid gland causing hypothyroidism, 242
- Goodman, B., et al. High flow whole body hemodilution perfusion: acid base, renal, electrolyte and body fluid alterations, 111
- Greenspan, E. M., Thio-TEPA and methotrexate chemotherapy of advanced ovarian carcinoma, 52
- Gribetz, I. et al. Tuberculous mediastinal adenopathy simulating neoplasm, 479
- Griboff, S. I., et al. Buccal androsterone therapy of hirsutism: A preliminary report, 179
- Gross, S. Contralateral trigeminal neuralgia in meningiomas of the cerebellopontine angle, 343
- The history of carotid artery ligation, 221
- H**ARKEN, Dwight, E. Coronary artery disease: rest, repair or replacement, 541
- Heiman, M. The responsibility of being an obstetrician and gynecologist, 350

- Hemodynamic abnormalities in shock. (W. Shoemaker), 451
- Hemoptysis. (CPC), 307
- Hemorrhage
intraoperative, (M. A. Naqvi et al), 396
jejunal submucosal following anti-coagulant therapy. (Rad. Notes), 328
- Hernia
indirect, traumatic diaphragmatic, 287
- High flow whole body hemodilution perfusion: acid base, renal, electrolyte and body fluid alterations. (Kahn et al), 111
- Hirsutism: (S. I. Griboff, et al.), 179
- History of carotid artery ligation (S. Gross), 221
- Hypothyroidism, (D. Sirota, et al.), 242
- I**MMUNOFLUORESCENT investigation of vascular lesions, report of a case with thrombotic thrombocytopenic purpura and systemic lupus erythematosus. (L. I. Alpert), 165
- Inborn errors of metabolism. (R. M. Sturman), 489
- Infanticide. (S. S. Asch), 214
- Initial contact with the cancer patient—some psychiatric considerations. (R. S. Blacher, et al), 423
- Institutional care facilities for older people in New York City. (M. Rogin et al), 358
- Intestine
obstruction caused by extrinsic benign myomata. (I. Parnes), 417
obstruction and splenosis (Unusual Problems in Surgery), 534
small, effect of varying fat diets, (A. M. Gelb), 429
- Intraoperative hemorrhage as a complication of acute ruptured cholecystitis. (M. Naqvi, et al), 396
- Isoenzymes of creatine phosphokinase determined by acrylamide gel electrophoresis. (A. Wolintz, W. K. Engel, and T. F. Summers), 174
- J**ACOBS, L. D. Bilateral complete internal carotid artery occlusions in a patient with transient neurologic deficits, 518
- Jaundice. (CPC), 526
- Jaw, familial fibrosis. (Rad. Notes), 436
- Jejunal submucosal hemorrhage following anticoagulant therapy. (Rad. Notes), 328
- K**AHN, M. High flow whole body hemodilution perfusion: acid base, renal, electrolyte and body fluid alterations, 111
- Katz, J. F. Minimal Legg-Calve-Perthes disease, 408
- Keller, Rhona J. Gastric polyps—longterm follow-up. (Rad. Notes), 622
- Klatell, J. and Marbach, J. J. The temporomandibular joints: A survey of disorders and treatment methods, 228
- Klempner, Emanuel. Problems of sterilization, 595
- Klion, F. M., Editor. See Clinico-Pathological Conferences
- Korelitz, B. I. Prognosis of granulomatous colitis with onset in childhood, 1
- L**ACHMAN, R. Radiological notes, 436, 438
- Lasser, R. P., et al. Exercise in normal dogs under chloralose and urethane anesthesia, 265
- Legg-Calve-Perthes disease. (J. F. Katz), 408
- Leichtling, J. J., editor. See unusual problems in surgery
- Lesnick, Gerson. An incision and method of wound closure for radical mastectomy, 599
- Levin, P. et al. Contralateral trigeminal neuralgia in meningiomas of the cerebello-pontine angle, 343
- Lipoma, extrapleural. (Rad. Notes), 444
- Litwak, R. S., et al. High flow whole body hemodilution perfusion: Acid base, renal, electrolyte and body fluid alterations, 111
- Liver, pediatric aspects of organellar pathology of. (H. Popper), 155
- Lyon, L. J. Coomb's positive hemolytic anemia due to penicillin, 258
- M**ALABSORPTION syndrome. (R. M. Sturman), 489
- Marbach, J. J. et al. The temporomandibular joints: A survey of disorders and treatment methods, 228
- Mastectomy, incision and method. (G. Lesnick), 599
- Medicaid. (M. Rogin et al), 358
- Medium chain triglycerides. (R. M. Sturman), 489
- Meningioma. (P. Levin et al), 343
- Meningitis, eosinophilic. (S. Gendelman), 578
- Metastatic infiltration of the thyroid gland causing hypothyroidism. (D. Sirota, et al.), 242
- lesion of the colon-primary in the stomach. (Rad. Notes), 635
- lesions to the colon-3 cases. (Rad. Notes), 639
- Minimal Legg-Calve-Perthes disease. (J. F. Katz), 408
- Moseley, J. et al. Congenital abnormalities of the small bowel, 14
- Myocardial infarction, acute, relationship with recent coronary artery occlusion. (I. Chapman), 149
- Myomata, benign. (I. Parnes), 417
- Myosarcoma
recurrent small bowel (Rad. Notes), 102
- Myxedema. (D. Sirota, et al), 242
- N**AQVI, M. A. et al. Intraoperative hemorrhage as a complication of acute ruptured cholecystitis, 396
- Neurofibroma, extrapleural. (Rad. Notes), 443

Neuropathy, diabetic, of the upper extremities, (M. Ellenberg), 134
ulcer, (M. Ellenberg), 585

Newborn
gastric perforation, 300

OBITUARY:

Feitelberg, Sergei, 108
Gadboys, Howard, 329
Schick, Bela, 211

Obstetrician and gynecologist, responsibility, (M. Heiman), 350

Occlusion, recent coronary artery, and acute myocardial infarction, relationships of, (I. Chapman), 149

Organelle pathology, pediatric aspects of in the liver, (H. Popper), 155

Ovarian

Thio-TEPa and methotrexate chemotherapy in advanced ovarian carcinoma, (Greenspan), 52

PANCYTOPENIA and chronic pulmonary disease in an elderly man (clinico-pathological conference), 86

Parnes, I. H. Intestinal obstruction caused by extrinsic benign myomata, 417

Peck, H. M., editor. See radiological notes
Pediatric aspects of organelle pathology of the liver, (H. Popper), 155

Penicillin, Coombs' positive hemolytic anemia due to, (L. J. Lyon), 258

Periosteal
bone tumors, (R. Zaretsky), 274

Peripheral ischemia, severe, (A. Singer, et al.), 234

Physiologic derangements in shock, (W. Shoemaker), 451

Polenz, J., et al. Psychotherapeutic drugs—patterns of use, 246

Polymyalgia rheumatica, (S. Davison, et al.), 473

Polyps, gastric, (Rad. Notes), 622

Popper, H. Pediatric aspects of organelle pathology of the liver, 155

Current trends in curriculum redesign, 332

Post-partum reactions, (S. S. Asch), 214

Problems of sterilization, (E. Klempner), 595

Prognosis of granulomatous colitis with onset in childhood, (Korelitz), 1

Psychiatry
responsibility of being an obstetrician and gynecologist, (M. Heiman), 350

Psychopharmacology, (J. Polenz, et al.), 246

Psychotherapeutic drugs—patterns of use, (J. Polenz, et al.), 246

Pulmonary

disease in an elderly man with pancytopenia (CPC), 86

RABINOWITZ, J. et al. Congenital abnormalities of the small bowel, 14
Tuberculous mediastinal adenopathy simulating neoplasm, 479

Radical local surgery in diabetic gangrene, (A. Singer et al), 390

Radioisotope

Therapy: (Wasserman & Glass), 68
Radiological Notes, Claude Bloch and Harvey Peck, Co-Editors

aneurysm of the splenic artery mimicking an intramural tumor of the stomach, 447

aneurysmal bone cyst with documented subperiosteal origin, 192

asphyxiating thoracic dystrophy, 438

bilateral Wilm's tumors, 100

carcinoma in sigmoid blind loop, 318
chronic osteomyelitis Brodie's abscess, 206

colonic bezoar due to serutan, 323

eggshell foreign body in subglottic region evident on chest roentgenogram, 98

extrapleural lipoma, 444

extrapleural neurofibroma, 443

familial fibrosis of the jaw, (Cherubism), 436

gastric carcinoma: 3½ year follow-up, 630

gastric leiomyosarcoma with remarkable progress over a two year period, 199

gastric polyps—long-term followup report of two cases, 622

jejunal submucosal hemorrhage following anticoagulant therapy, 328

metastatic lesions to the colon—report of 3 cases, 639

metastatic lesion of the colon—primary in the stomach, 635

pedunculated adenomatous polyp at the ligament of Treitz, 104

recurrent small bowel myosarcoma, 102

small bowel postoperative blind loop causing anemia, 321

ureterocele, duplex collecting system, and obstructive uropathy, 196

Relationships of recent coronary artery occlusion and acute myocardial infarction, (I. Chapman), 149

Responsibility of being an obstetrician and gynecologist, (M. Heiman), 350

Retinitis pigmentosa, (R. M. Sturman), 489

Rheumatic heart disease, (CPC), 307

Rinzler, C., et al. Wrist-cutting and suicide, 485

Rogin, M. et al. Institutional care facilities for older people in New York City, 358

Rosen, A. L. et al. Development and goals of a trauma and shock research center, 451

Rossi, G., et al. Early results with 20 femoro-popliteal vein bypass grafts for severe peripheral ischemia, 234

Radical local surgery in diabetic gangrene, 390

SCHEIN, A. J. Evolution and Pathogenesis of discogenic spine pain and associated radiculitis as seen in the New York City Fire Department, 371

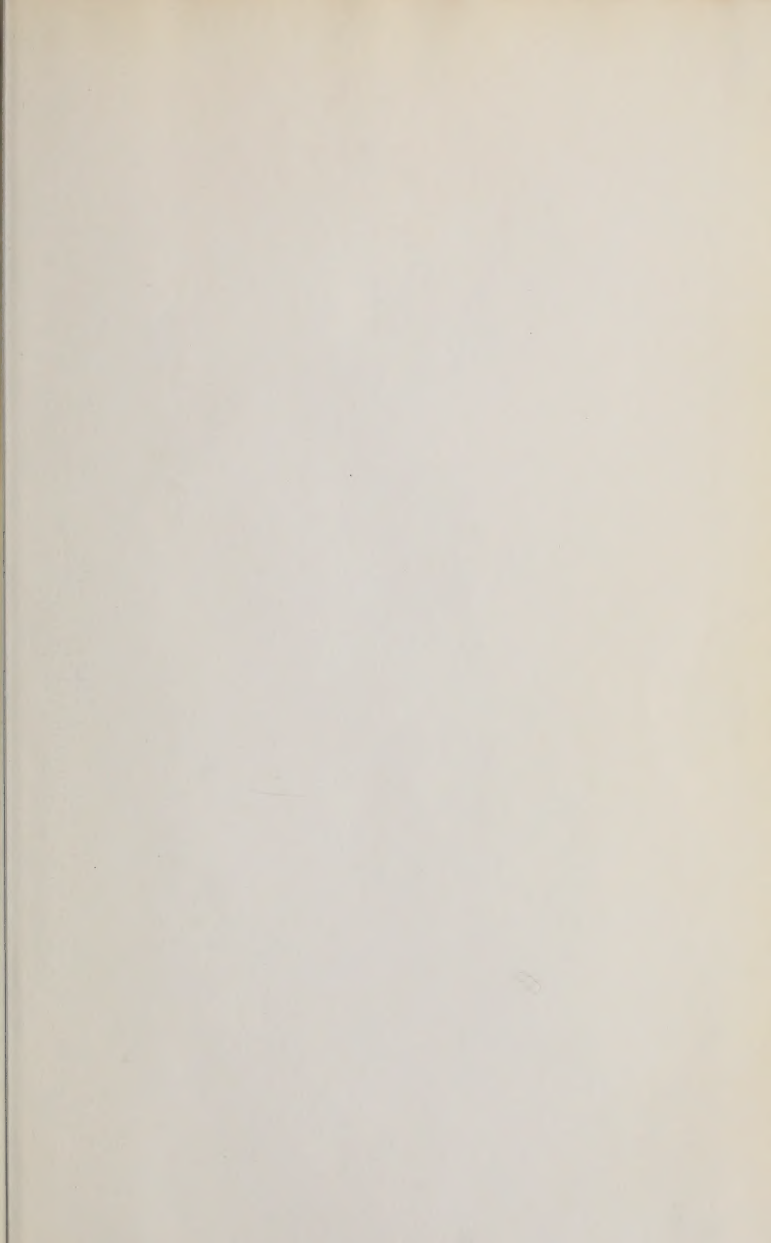
Schick, Bela. Obituary, 211

Schizophrenia (J. Polenz, et al.), 246

Wrist-cutting (D. Rinzler et al), 485

- Serutan, causing colonic bezoar. (Rad. Notes), 323
- Shapiro, D. A., et al. Wrist-cutting and suicide, 485
- Shock. (W. Shoemaker, et al), 451
- Sickle cell anemia complicated by anuria. (CPC), 610
- Singer, A. et al. Early results with 20 femoro-popliteal vein bypass grafts for severe peripheral ischemia, 234
- Radical local surgery in diabetic gangrene, 390
- Sirota, D. K., et al. Metastatic infiltration of the thyroid gland causing hypothyroidism, 242
- Spiera, H., et al. Concepts and treatment in polymyalgia rheumatica, 473
- Splenosis and intestinal obstruction, (Unusual Problems in Surgery), 534
- Steatorrhea. (R. N. Sturman), 489
- Stein, P. D., et al. Exercise in normal dogs under chloralose and urethane anesthesia, 265
- Sterilization, problems of. (E. Klempner), 595
- Stomach, metastatic lesion of colon, primary in the stomach. (Rad. Notes), 635
- Sturman, R. M. The Bassen-Kornzweig syndrome: 18 years in evolution, 489
- Sudden unexplained death in infants ("S.U.D."). (S. S. Asch), 214
- Suicide, wrist-cutting. (C. Rinzler, et al), 485
- Summers, T. F., et al. Isoenzymes of creatine phosphokinase determined by acrylamide gel electrophoresis, 174
- Systemic lupus erythematosus and thrombotic thrombocytopenic purpura: Report of a case with immunofluorescent investigation of vascular lesions. (L. I. Alpert), 165
- TEICH**, Eugene, Afebrile bacterial endocarditis, 566
- Temporomandibular joints: A survey of disorders and treatment methods, (J. Klatell, et al), 228
- Testosterone, urinary. (S. Griboff, et al), 179
- Therapy with radioisotopes: a general survey (excluding iodine). (Wasserman et al), 68
- Thio-TEPa and methotrexate chemotherapy of advanced ovarian carcinoma (Greenspan), 52
- Thoracic dystrophy. (Rad. Notes), 438
- Thrombotic thrombocytopenic purpura and systemic lupus erythematosus: Report of a case with immunofluorescent investigation of vascular lesions. (L. I. Alpert), 165
- Thyroid
- Metastatic infiltration (D. Sirota, et al), 242
- Transient ischemic episodes, and neurologic deficits. (L. D. Jacobs), 518
- Trauma. (W. Shoemaker, et al), 451
- Trigeminal neuralgia. (P. Levin, et al), 343
- Tuberculous mediastinal adenopathy simulating neoplasm. (J. G. Rabinowitz, et al), 479
- Tumors
- bone, of periosteal origin. (R. Zaretsky), 274
- myomata (I. Parnes), 417
- Turner, H. et al. Institutional care facilities for older people in New York City, 358
- UNGER**, A. H., et al. Metastatic infiltration of the thyroid gland causing hypothyroidism, 242
- Unusual Problems in Surgery
- gastric perforation in a newborn, 300
- indirect traumatic diaphragmatic hernia, 287
- splenosis and intestinal obstruction, 534
- Urethane. (P. D. Stein, et al), 265
- WASSERMAN**, L. R. et al. Therapy with radioisotopes: A general survey (excluding iodine), 68
- Wilm's tumors
- bilateral (Rad. Notes), 100
- Winkelstein, C., et al. The initial contact with the cancer patient—some psychiatric considerations, 423
- Wolintz, A. H., et al. Isoenzymes of creatine phosphokinase determined by acrylamide gel electrophoresis, 174
- Wrist-cutting and suicide. (C. Rinzler, et al), 485



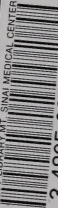




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